

***United States Court of Appeals
for the Second Circuit***



APPENDIX

74-2477

UNITED STATES COURT OF APPEALS

FOR THE SECOND CIRCUIT

STERLING DRUG INC., WINTHROP PRODUCTS, INC.
and BREON LABORATORIES, INC.,

Plaintiffs-Appellants,

- against -

CASPAR W. WEINBERGER, Secretary of Health, Education and
Welfare, and ALEXANDER M. SCHMIDT, Commissioner of
Food and Drugs,

Defendants-Appellees.

JOINT APPENDIX

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Appellees

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Attorney



PAGINATION AS IN ORIGINAL COPY

JOINT APPENDIX

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A. 1

CIVIL DOCKET
UNITED STATES DISTRICT COURT

Jury demand date:

JUDGE PIERCE

D. C. Form No. 105 Rev.

TITLE OF CASE

ATTORNEYS

STERLING DRUG INC.,
WINTHROP PRODUCTS, INC. and
BREXON LABORATORIES, INC.

v.

CASPAR W. WEINBERGER, Secretary of
Health, Education and Welfare, and
ALEXANDER M. SCHMIDT, Commissioner
of Food and Drugs,

For plaintiff:

Rogers, Hoge & Hills
90 Park Ave. N.Y.C. 10016 953-9200

For defendant:

STATISTICAL RECORD

COSTS

DATE

NAME OR
RECEIPT NO.

REC.

J.S. 5 mailed

Clerk

J.S. 6 mailed

Marshal

Basis of Action: Enjoin

Docket fee

Proceeding by the F.D.A.
as invalid

Witness fees

DOCKET ENTRIES BELOW

A. 1

DATE	PROCEEDINGS	Date Order Judgment
ap 20-74	Filed complaint and issued summons.	
t. 2-74	Filed pliff's affidavit - Order to Show Cause for a Preliminary Injunction-Ret. 10-9-74	
t. 2-74	Filed pliffs' memorandum in support of motion for preliminary injunction.	
Oct 8-74	Filed defts' affidavit in opposition to Pliffs' motion for a Preliminary Injunction-Ret. 10-9-74.	
Oct 8-74	Filed defts' memorandum of law in opposition to Pliffs' motion for a Preliminary Injunction Ret. 10-9-74.	
ct. 11-74	Filed defts' proposed Findings of Fact & Conclusions of Law.	
t. 10-74	Filed summons & return, served deft. Coma. of Food & Krugs by William Weigel on 10-3-74 & by registered mail to the Coma. Food & Drugs, Maryland. Served deft. Sec'y of Health by William Weigel & by registered mail to U.S. Atty Gen'l 10-3-74.	
ct 10-74	Before Pierce, J. Hearing on Order to Show Cause for preliminary injunction begun & consolidated with trial on merits. Trial concluded. Dec. Reserved	
t. 29-74	Filed stip & order extending pliffs' time to file data on which they rely to justify a hearing regarding defts' notice entitled "Alevaire to 15 days after the filing of the decision of this Court on pliffs' motion for preliminary injunction--Pierce, J.	
t. 1-74	Filed OPINION #41,381-The pliffs' application for an injunction is denied and the complaint is dismissed. The foregoing shall constitute this Court's findings of fact & conclusions of law pursuant to Rule 52(a) of the F.R.C.P. Submit order on two days notice.--Pierce, J.	
6-74	Filed transcript of record of proceedings, dated 8-15-74	
6-74	Filed transcript of record of proceedings, dated 10-10-74	
ev 6-74	Filed Pliffs. Notice of Appeal from judgment entered 11/6/74. (mailed notice)	
Nov. 22-74	Filed plaintiffs' reply letter to defendants' Memorandum (letter dated Oct. 15-74).	

United States District Court

FOR THE
SOUTHERN DISTRICT OF NEW YORK

CIVIL ACTION FILE NO. _____

STERLING DRUG INC.,
WINTHROP PRODUCTS, INC. and
BREON LABORATORIES, INC.,

Plaintiffs

v.

CASPAR W. WEINBERGER, Secretary of
Health, Education and Welfare, and
ALEXANDER M. SCHMIDT, Commissioner
of Food and Drugs,

Defendants

SUMMONS

74 Civ. 14282 (LWP)
(Pierce)

To the above named Defendant :

You are hereby summoned and required to serve upon Rogers Hoge & Hills

plaintiff's attorney , whose address is 90 Park Avenue, New York, New York 10016

an answer to the complaint which is herewith served upon you, within 60 days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint.

/s/ Raymond F. Burr
Clerk of Court.
/s/ B. Edwards
Deputy Clerk.

Date: September 30, 1974

[Seal of Court]

NOTE:--This summons is issued pursuant to Rule 4 of the Federal Rules of Civil Procedure.

COMPLAINT A.5

the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §301 et seq. ("the Act"). Defendant Weinberger has a place of business in the District of Columbia.

5. Defendant Alexander M. Schmidt ("Schmidt") is Commissioner of Food and Drugs and has been delegated responsibility for enforcing the Act. Defendant Schmidt has a place of business in Rockville, Maryland.

6. The matter in controversy herein exceeds the sum or value of \$10,000, exclusive of interest and costs and arises under the United States Constitution, Amendment V, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §301 et seq., Administrative Procedure Act, 5 U.S.C. §551 et seq., and 28 U.S.C. §§1331, 1332, 1337, 1651, 2201 and 2202. Venue lies in this District pursuant to 28 U.S.C. §1391(e).

FIRST CAUSE OF ACTION

7. Sterling and Winthrop are holders of approved new-drug applications (NDA's) Nos. 8-530 and 10-613 for the prescription drug Alevaire, a mucoevacuant aerosol preparation which is indicated for use in chronic, obstructive lung conditions to aid in the evacuation of broncho-pulmonary secretions. Alevaire is composed of an active ingredient tyloxapol, in a vehicle of water, 2 percent sodium bicarbonate and 5 percent glycerine. Alevaire has been marketed in this country under approved NDA's since 1952 and since 1965, marketing and distribution has been the responsibility of Breon, a wholly owned subsidiary of Sterling. Winthrop, also a wholly owned subsidiary of

COMPLAINT A.6

Sterling, has responsibility for the marketing and distribution of Alevaire outside the United States.

8. By notice dated December 1, 1968, the Food and Drug Administration ("FDA") issued a proposal to withdraw approval of the NDA's for Alevaire on grounds of lack of proof of effectiveness. Plaintiffs duly compiled and submitted evidence confirming the effectiveness of Alevaire, including, but not limited to, two new clinical studies which they contended were adequate and well-controlled. One study, by Drs. William F. Miller and Pedro Paez ("the Miller-Paez study") compared Alevaire to water and saline, the two most commonly used mucoevacuant agents. The other study, by Dr. Burton M. Cohen, compared Alevaire to water. These studies were submitted in June 1970.

9. By order dated August 27, 1971, FDA stated that in its opinion, the Miller-Paez and Cohen studies were not adequate and well-controlled, and ordered the withdrawal of approval of the NDA's for Alevaire for lack of proof of effectiveness. A copy of said withdrawal order is attached hereto as Exhibit 1. Plaintiffs then appealed from that order to the United States Court of Appeals for the Second Circuit in Docket 71-1898. After the record had been filed and plaintiffs herein (petitioners therein) had printed and filed the record and briefs, defendants herein (respondents therein) confessed error and moved to remand the matter to the FDA for further consideration. The motion was granted and in January 1972 the matter reverted to the FDA.

10. FDA took over a year, until March 2, 1973, to issue a new order notwithstanding that the evidence which

COMPLAINT A. 7

FDA reviewed had not changed in any way. FDA's new order repeated the assertions that the Miller-Paez and Cohen studies were not adequate and well-controlled and again ordered the withdrawal of approval of the NDA's for Alevaire on the grounds of lack of proof of effectiveness pursuant to Section 505(e)(3) of the Act, 21 U.S.C. §355 (e)(3). A copy of the withdrawal order of March 2, 1973 ("March order") is attached hereto as Exhibit 2.

11. The principal ground set forth in the March order for rejecting the Miller-Paez and Cohen studies was that:

"In the case of Alevaire, a comparison of the results of use of the drug itself with an inactive preparation designed to resemble Alevaire must be utilized. Thus, to establish effectiveness, the studies relied on would have to at least compare Alevaire to a product containing an aqueous solution of 2 percent sodium bicarbonate and 5 percent glycerine. None of the studies or articles cited make such a comparison."

Specifically, for each of the Miller-Paez and Cohen studies, the order stated:

"Most importantly, the test did not compare Alevaire to a proper control, e.g. Alevaire minus tyloxapol, in other words a solution of 2 percent sodium bicarbonate, 5 percent of glycerine and 93 percent water."

12. Plaintiffs promptly filed a Petition for Reconsideration, supported by the affidavits of recognized experts in the field as well as by affidavits from Drs. Miller and Cohen. Each stated his opinion that, while the control suggested by FDA in its order was suitable, the controls utilized by Drs. Miller and Cohen were equally valid.

COMPLAINT A. 8

if not preferable. Plaintiffs also pointed out that the controls employed were appropriate under the Act and FDA's own regulations promulgated thereunder, 21 C.F.R. 136.12(a), 136.12(b)(1), 136.12(b)(2), 136.12(b)(3), 136.12(b)(4) (now recodified as 21 C.F.R. 314.111) and that, in its first withdrawal order in August 1971, FDA had confirmed that water was an appropriate control.

13. FDA informed plaintiffs that the Petition for Reconsideration would be denied, and thereafter plaintiffs again appealed to the United States Court of Appeals for the Second Circuit, in Docket 73-1628. On June 14, 1973, after exclusive jurisdiction had vested in the Court of Appeals, FDA unilaterally revoked its withdrawal order of March 2, 1973 (Exhibit 2) and simultaneously moved in the Court of Appeals to dismiss the appeal. A copy of the order of revocation is attached hereto as Exhibit 3.

14. On August 7, 1973, while the motion to dismiss the appeal was pending, FDA issued a third withdrawal order. ("August order") This order abandoned the grounds stated in the March order, but instead, and for the first time, proposed the novel theory that Alevaire was a fixed-combination drug within the meaning of 21 C.F.R. § 314.116, for which the only proof of effectiveness would be a study comparing "Alevaire, Alevaire less tyloxapol, Alevaire less sodium bicarbonate, Alevaire less tyloxapol and sodium bicarbonate, water, etc." A copy of this order is attached hereto as Exhibit 4.

15. Defendants' motion to dismiss plaintiffs' appeal from the March order was denied, and when plaintiffs

appealed from the August order as well in Docket 73-2481, the two appeals were consolidated.

16. By decision dated May 2, 1974, the Court of Appeals reinstated approval of the NDA's for Alevaire. As to the appeal from the March order, the Court stated that this order "for the first time" voiced the opinion that the only proper "control" against which to test Alevaire was:

"Alevaire minus tyloxapol. In other words, a solution of 2% sodium bicarbonate, 5% glycerine and 93% water."

The Court noted that plaintiffs' Petition for Reconsideration of the March order contained:

"an extensive rebuttal of the grounds on which the order was based, which, in light of subsequent events, was apparently well taken."

As to FDA's third withdrawal order of August, 1973, the Court stated that:

"This third order abandoned the grounds on which the prior two orders of March 2, 1973 and August 27, 1971 had been based."

The Court then concluded as to the March order:

"The March 2, 1973 Order"

The appeal from the March 2, 1973 order denying a hearing and withdrawing approval of the Alevaire NDA's is in a curious posture. Subsequent to the taking of the appeal, the March 2 order was terminated by the FDA's order of June 14, 1973 which granted petitioners' application for reconsideration of their requests for a hearing and reinstated approval of the Alevaire NDA's."

The respondents' brief states: "We confessed error in that order [of March 2, 1973] before

COMPLAINT A. 10

this Court on November 9, 1973 and petitioners objected. We again confess error, with the hope that petitioners will not look a gift horse in the mouth a second time.'

Concededly erroneous though it was, and despite the continuing pendency of the appeal, the March 2 order is no longer in force and effect. We fail to see what relief could be granted to petitioners under these circumstances. The appeal from the March 2, 1973 order must be dismissed as moot."

A copy of the aforesaid decision is attached hereto as Exhibit 5.

17. As shown by said decision, the August order was set aside on the grounds that defendants, by raising the fixed-combination theory for the first time in that order, had arbitrarily violated plaintiffs' rights. The Court stated:

"Viewed in the light of the extended prior proceedings and the two prior orders of withdrawal without a hearing on quite different grounds, terminated by the FDA only after petitioners had appealed to this Court, it is apparent that the FDA arbitrarily disregarded the requirements of the statute and its own regulations. The order of August 7, 1973 is invalid and must be set aside and the original approval of the NDA's for Alevaire reinstated."

The Court concluded:

"While there is little in the record now before us to support the proposition that Alevaire is a fixed combination drug within the meaning of 21 C.F.R. 3.86, it is not for this Court to pass on the question on this appeal. If the FDA proposes to withdraw approval of the NDA's for Alevaire on the ground that it is ineffective as a fixed combination drug, it must follow the procedure required by the statute and regulations."

COMPLAINT A. 11

It must give the petitioners notice of the specific grounds proposed for withdrawal, an opportunity to present evidence showing that they are entitled to a hearing, and a hearing if that is shown to be required. The FDA may then determine the question on a full and proper record, subject, of course, to petitioners' right of appeal to this Court from an adverse determination." (Emphasis added)

18. Defendants have not sought to appeal the aforesaid decision of the Court of Appeals and their time to do so has expired.

19. As a result of the foregoing, the parties hereto have litigated defendants' contention that the effectiveness of Alevaire can appropriately be tested only against its vehicle, namely, a control solution of 2% sodium bicarbonate, 5% glycerine and 93% water. As set out above, it is clear that defendants have previously conceded the erroneous nature of this contention and have formally abandoned said contention.

20. Said formal concession and said abandonment made in and before the Court of Appeals are binding upon defendants.

21. The decision of the Court of Appeals makes clear that defendants' said contention has been abandoned as erroneous and that the proceeding based therein has been "terminated." The decision does not contemplate and by its terms bars any new proceeding based on said contention.

22. Nevertheless, by Notice dated August 1, 1974 appearing in the Federal Register of August 13, 1974, 39 Fed. Reg. 29013-29014, defendants have issued a new proposal

to withdraw approval of the NDA's for Alevaire. Said proposal is based, in part, on the proposition that:

"evidence must be presented that Alevaire is more effective than its admittedly active vehicle. Development of such evidence would require a two-group trial: patients treated with the vehicle (water, bicarbonate, and glycerin) alone vs. patients treated with Alevaire. In this instance, a comparison of Alevaire with water or saline [as in the Miller-Paez and Cohen studies] does not address the question of whether tyloxapol is an active drug, since any difference seen favoring Alevaire could be the result of the bicarbonate."

A copy of said Notice is attached hereto as Exhibit 6.

23. Pursuant to said Notice, plaintiffs are required to present evidence to defendants by October 15, 1974 or face withdrawal of approval of their NDA's. Plaintiffs, by their attorneys, requested an extension of said date, which request has been denied by defendants.

24. Insofar as the new Notice is based on an issue already litigated, previously conceded by defendants to be erroneous, defendants are barred by the doctrines of res judicata and/or collateral estoppel from again raising said issue.

25. By reason of their formal abandonment and concession on said issue in the prior litigation, defendants are estopped from again raising said issue in their new Notice.

26. The pendency of said improper and unlawful proceeding is and, unless enjoined by this Court, will continue to cause irreparable damage to the reputation and sales of plaintiffs' product, Alevaire, and to the reputation of plaintiffs and will cause plaintiffs to incur the time and expense of participating in said improper and unlawful proceeding.

COMPLAINT A. 13

SECOND CAUSE OF ACTION

27. Repeat and reallege as if fully set forth herein the allegations contained in paragraphs "1" - "18", "23" and "26" above.

28. As stated by the Court of Appeals

"There is little in the record now before us to support the proposition that Alevaire is a fixed combination drug within the meaning of 21 C.F.R. 3.86 ..." (Slip Op. p. 3137)

Nevertheless, defendants in their new Notice, in addition to the grounds described in the First Cause of Action, also seek to withdraw approval of the NDA's for Alevaire on the theory that Alevaire may be a fixed-combination drug and that appropriate test data for Alevaire as a fixed-combination drug are lacking.

29. In thus proceeding against plaintiffs, defendants are purportedly acting pursuant to Section 505(e) (3) of the Act, 21 U.S.C. §355(e) (3), which provides that approval of an NDA may be withdrawn by the Secretary if, "after due notice and opportunity for hearing ... the Secretary finds:"

"on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof ..."
(Emphasis added)

Accordingly, defendants must possess the requisite "new information" before they may proceed to withdraw approval

COMPLAINT A. 14

of the NDA's for Alevaire.

30. Defendants' new Notice fails to specify what "new information," as required by the Act, forms the basis for their proposal.

31. Upon information and belief, defendants possess no "new information" as required by the Act, sufficient to warrant institution and maintenance of the proceeding.

32. Defendants' new Notice, insofar as it proposes to withdraw approval of the NDA's for Alevaire on the grounds that the drug is a fixed-combination, is therefore invalid in that defendants possess no "new information" as required by statute to support the contention that the drug is a fixed-combination and is ineffective as such.

WHEREFORE, plaintiffs pray for judgment:

A. Declaring that defendants are barred by the doctrines of res judicata and/or collateral estoppel and are estopped by their prior admissions and concessions from proceeding to withdraw approval of the new-drug applications for plaintiffs' product Alevaire on the grounds that proof of effectiveness must be demonstrated by comparing Alevaire to its vehicle, namely to water, sodium bicarbonate and glycerine.

B. Declaring that defendants are barred by statute, 21 U.S.C. §355(e), from proceeding to withdraw approval of the new-drug applications for plaintiffs' product Alevaire on the ground that it is a fixed-combination product within the meaning of 21 C.F.R. 3.86, and is ineffective as such, in that defendants lack the requisite

"new information" to support said contention.

C. Preliminarily, during the pendency of this action, enjoining defendants, their officers, agents, servants, employees, and attorneys, and those persons in active concert or participation with them from proceeding with the proposal to withdraw approval of the new-drug application for plaintiffs' product Alevaire pursuant to Notice dated August 1, 1974 and appearing at 39 Fed. Reg. 29013-29014 (August 13, 1974) and then permanently enjoining defendants, their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them from proceeding pursuant to the aforesaid Notice or with any proceeding to withdraw approval of the new-drug applications for plaintiffs' product Alevaire on the grounds that proof of effectiveness must be demonstrated by comparing Alevaire to its vehicle, namely, to water, sodium bicarbonate and glycerine, or on the grounds that Alevaire is a fixed-combination drug and is ineffective as such, in the absence of the "new information" required to support such a claim.

D. For such other and further relief as the Court may deem just and proper.

Dated: New York, New York
September 30, 1974

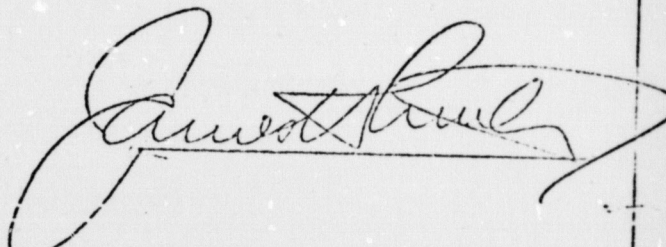
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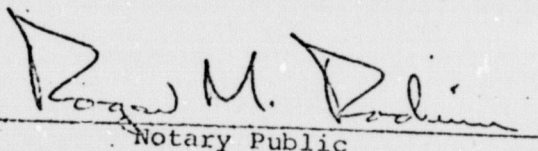
COMPLAINT A. 16

STATE OF NEW YORK)
: ss.:
COUNTY OF NEW YORK)

JAMES H. LUTHER, being duly sworn, states that he is Vice President of Sterling Drug Inc., one of the plaintiffs named in the foregoing complaint; that he has read the complaint and knows the contents thereof; that the allegations are true, except as to the matters stated therein to be alleged upon information and belief, and as to those matters he believes them to be true.



Subscribed and sworn to before
me this 30th day of September, 1974.



Notary Public

ROGER M. RODWIN
Notary Public, State of New York
No. 31-8614185
Qualified in New York County
Commission Expires March 30, 1976

S336

NOTICES

PROVISIONALLY LISTED COLOR ADDITIVES

Notice Concerning Certain Scientific Investigations

Section 8.501 of the color additive regulations (21 CFR 8.501), designates those color additives that are provisionally listed pursuant to section 203(b) of the Color Additive Amendments of 1960 (sec. 203(b), Public Law 86-618, 74 Stat. 405; 21 U.S.C. 376, note). Section 203 provided for provisionally listing certain color additives on an interim basis pending completion of scientific investigations needed as a basis for making determinations as to whether they should or should not be listed under section 706 of the Federal Food, Drug, and Cosmetic Act (sec. 706, 74 Stat. 399-403; 21 U.S.C. 376).

It has been determined that, for those uses of color additives listed in paragraphs (a) and (b) of § 8.501 of the color additive regulations which involve ingestion because of use in products such as food, drugs for internal use, and cosmetic lipsticks, petitions for regulations under section 706 of the act shall include reports of studies for teratological potential and reports of multigeneration reproduction studies in animals adequate to show whether the color additive produces any adverse effects on reproduction. There being information at hand showing that such studies can be commenced promptly, it is reasonable to require that the final reports on teratological potential for color additives now provisionally listed in § 8.501 be filed with the Food and Drug Administration not later than October 1, 1972, and that the final reports on multigeneration reproduction studies be filed with FDA not later than July 1, 1973.

Any questions concerning teratogenic studies or reproduction studies may be taken up with the Food and Drug Administration pursuant to § 8.35(c) of the color additive procedural regulations (21 CFR 8.35(c)).

For a further extension of provisional listing beyond December 3, 1971, any person having the prescribed animal studies underway may file a request for a further extension with FDA. Such request shall be supported (1) by progress reports on the animal studies, and (2) by a statement estimating the date when a petition can be filed seeking a regulation under section 706 of the act. Current usage data showing the levels of use in specific foods or in classes of foods, the levels of use in specific drugs for internal use or in classes of internal drugs, and the levels of use in cosmetics subject to ingestion shall be submitted in support of such petition at the time it is filed.

The Commissioner may give consideration to the termination of a provisional listing of the color additives listed in paragraphs (a) and (b) of § 8.501 if (1) no request for an extension of the provisional listing is received prior to

the date the provisional listing expires; (2) the request for extension is not adequately supported by the information requested; or (3) any report, be it a progress report or a final report, shows that the color additive is unsafe under its proposed conditions of use. The Commissioner may also give consideration, where the scientific data so indicate, to reducing the aggregate use of a color in a provisional listing by eliminating or restricting certain uses in accordance with the procedure in § 8.11 (21 CFR 8.11).

Data in response to this notice should be addressed to the Food and Drug Administration, Bureau of Foods, Office of Compliance, Division of Petitions Processing, 200 C Street SW., Washington, DC 20204.

Dated: September 7, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 71-13366 Filed 9-10-71; 8:46 am]

[DESI 8530; Docket No. FDC-D-141; NDA Nos. 10-613 and 8-530]

WINTHROP PRODUCTS, INC., AND WINTHROP LABORATORIES

Alevaire; Notice of Withdrawal of Approval of New-Drug Applications

In an announcement published in the FEDERAL REGISTER of July 17, 1968 (33 FR 10227), Winthrop Products, Inc., holder of new-drug application No. 10-613 for Alevaire (Cyloxapol 0.125 percent) and Winthrop Laboratories, Division of Sterling Drug, holder of new-drug application No. 8-530 for Alevaire (Cyloxapol 0.125 percent), were notified of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's evaluation of the article as ineffective, and of the Food and Drug Administration's concurrence with the evaluation and its conclusions that there is a lack of substantial evidence that Alevaire will have the effect it purports and is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. Accordingly, the Commissioner of Food and Drugs noted his intent to initiate action to withdraw approval of the new-drug applications for Alevaire, and invited holders of the NDA's to submit any pertinent data.

After the announcement, Winthrop met with representatives of the Food and Drug Administration on August 13, 1968, to present arguments and additional evidence in support of the claimed effectiveness of Alevaire. The arguments and data were evaluated, but failed to provide any evidence of effectiveness derived from adequate and well controlled clinical investigations. On December 6, 1969, there was, therefore, published in the FEDERAL REGISTER (34 FR 19389), a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions

such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The foreign article provides occluded X-rays of high intensity which minimizes the exposure time required to obtain an X-ray diffraction pattern. We are advised by the Department of Health, Education, and Welfare (HEW) in its memorandum dated May 7, 1971, that the characteristics of the article described above are pertinent to the applicant's intended purposes. HEW further advises that it knows of no domestic X-ray camera which provides the pertinent characteristics of the article.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

SETH M. BOONER,

Director,

Office of Import Programs.

[FR Doc. 71-13428 Filed 9-10-71; 8:51 am]

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Food and Drug Administration

FD&C RED NO. 2

Color Additives; Notice Concerning the Timing of Data About Specific Uses

Preliminary data on reproduction studies with FD&C Red No. 2, one of the color additives provisionally listed, have recently come to the attention of the Food and Drug Administration. These data indicate that the aggregate use of this color may need to be lowered from the level at which it has been heretofore used. Section 706(b)(8) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 376(b)(8)) concerns those cases where it may be necessary to allocate the aggregate allowable safe tolerance of a color additive among uses.

Pursuant to § 8.11 of the color additive regulations (21 CFR 8.11), all persons interested in the use of FD&C Red No. 2 after December 31, 1971, are hereby notified to present their data as to all specific uses showing the amounts of this color proposed for continued use in foods, ingested drugs, and ingested cosmetics not later than October 31, 1971. The required data should be sent to the Food and Drug Administration, Bureau of Foods, Office of Compliance, Division of Petitions Processing, 200 C Street SW., Washington, D.C. 20204.

Dated: September 7, 1971.

CHARLES C. EDWARDS,

Commissioner of Food and Drugs.

[FR Doc. 71-13367 Filed 9-10-71; 8:46 am]

of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (e)) withdrawing approval of new-drug application Nos. 12-012 and 8-529 for Alevaire, and all amendments and supplements thereto, on the ground that there was a lack of substantial evidence to support the claims of effectiveness for the drug for the conditions for which it is prescribed, recommended, or suggested in the labeling.

Windrop Products, Inc., holder of NDA No. 10-012; Windrop Laboratories, Division of Sterling Drug Inc., holder of NDA No. 8-529; and Breon Laboratories, Inc., a firm marketing Alevaire in the United States, filed a written appearance and request for hearing on January 20, 1970.

Submitted with the request was a statement of grounds, including the medical documentation relied upon, arguments which contended that there was an unqualified right to a hearing, and the affidavits of six physicians and scientists attesting to the drug's effectiveness. Additional medical documentation was submitted by a letter dated May 7, 1970.

On June 5, 1970, in response to the May 8, 1970 Federal Register publication of procedural and interpretative regulations, a supplemental election for hearing was submitted, included in which was further medical documentation and a reiteration of the argument and reasons for a hearing as stated in the initial request for hearing. On August 13, 1970, one final medical document was submitted as a supplement to the January 20, and June 5 filings, and on March 10, 1971, the statement of the Medical Director of Breon Laboratories was received.

This presentation, as well as the medical documentation reviewed by the NAS-NRC panel and the medical documentation contained in both NDAs have been considered. The Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing and that the legal arguments are insubstantial.

Reasons for withdrawal of approval—
1. **The Drug.** Alevaire is a fixed combination aqueous solution of 0.125 percent tyloxapol, 2 percent sodium bicarbonate, and 5 percent glycerin.

It is recommended in the treatment of patients "with diseases and disorders of the lungs accompanied, or complicated, by excessive or thickened bronchopulmonary secretions," and is indicated also for persons having pulmonary diseases where "the normal mechanism for elimination of secretions is diminished or absent." . . .

The rationale for the drug has been variously described. In its initial NDA approval, it was described as a "mucolytic" drug. . . . It was also described as having a "liquefying effect on excessive or thickened mucous secretions, thereby aiding the patient in their elimination. The rationale, as stated in the labeling submitted for review by the NAS-NRC panel, is that the drug acts as a detergent

aerosol facilitating the removal of the pulmonary secretions allowing for excretion by normal processes by lowering or reducing the surface and interfacial tensions and reducing their viscosity.

Alevaire is recommended for administration in an undiluted form by an aerosol nebulizer delivering a fine mist to the patient in an open tent, group tent or incubator. Where short periods of therapy are indicated, 10 to 20 ml are recommended to be administered by a face mask, positive pressure breathing machines, or oral or nasal spray apparatus.

2. **Clinical Evidence to Support the Claims of Effectiveness.** Petitioners have presented summaries of 19 published and unpublished reports, and have cited nine additional articles, described as establishing that Alevaire is effective for use, and, that contrary to the "clinical impression" of the NAS-NRC panel, clinical and other evidence establishes Alevaire to be more effective than water.

Of the 19 reports summarized, none may be classified as an adequate and well-controlled clinical investigation. Twelve of these reports involve nothing more than discussions of clinical impressions and observations concerning the use of Alevaire, in vitro experiments, or articles mainly devoted to a discussion of medical problems. These 12 reports are as follows: One consisted of a collection of case reports on 17 adults treated by several doctors, in which the authors state that " . . . this does not pretend to be a controlled study." Another was a report of an in vitro study of the viscosity of sputum, bronchial pus and amniotic fluid, together with statements of the author as to Alevaire's effectiveness based upon his clinical use of the drug. Another evaluated resuscitation of infants born by Cesarean section, and contained undocumented statements as to the usefulness of Alevaire in such treatment. Two additional reports were based on clinical impressions from use of the drug in a number of individual cases, and were testimonial in nature. Three reports consisted of discussions of the treatment of laryngitis in children, general pulmonary problems, and bronchopulmonary disorder, in which Alevaire was employed in treatment and is discussed only incidentally. Two of the articles were devoted to discussions and clinical impressions of aerosol therapy agents in general, and references to Alevaire were generalized and consisted of undocumented clinical impressions. One report was of an in vitro experiment of the effect of the drug as a surface-active agent, and another, a study of Alevaire conducted on cats, an animal whose respiratory tract differs from that of man.

The seven remaining articles were reports of studies conducted with Alevaire. These, however, provide no substantial evidence of efficacy. These seven consisted of five completed and two preliminary studies, and each was deficient to varying degrees in meeting the criteria

for adequate and well controlled clinical trials, as follows. In one, an unpublished preliminary study, the investigators saturated the incubators of newborn infants with Alevaire. The conclusion that the therapy was of value, however, was based on general clinical observations rather than documented results. In another incomplete and unpublished study, a crossover comparison between Alevaire and isotonic saline, the "Interim report" of the investigator was that it was his "impression" on the basis of "preliminary information" that Alevaire is more effective than saline in increasing volume of sputum.

In one published study, Alevaire was administered to 360 patients with varying pulmonary conditions, and the therapeutic response was measured by general physical condition after treatment, characteristics of the sputum, and changes in respiratory effect. There were no controls and the study yielded no meaningful data on therapeutic response. Similarly, another study of children with acute bronchitis is lacking in the criteria necessary for a controlled study by failing to indicate diagnostic criteria or patient selection, methods of observation, measurement of variables, quantitation of results, and information as to the substance which may have been used as a control. Of the three remaining studies, one is an unpublished single blind crossover comparison of the effectiveness of Alevaire with water which appeared to indicate that Alevaire significantly increased both sputum volume and weight. The study, however, failed to state the method of patient selection, and the diagnostic criteria for bronchial asthma and chronic bronchitis was not stated. Further, no assessment of subjective response, nor steps taken to minimize bias were included in the study, nor was there documentation of the levels and methods of blinding. Another study, an unpublished crossover study in which Alevaire was reported as more effective than saline or water, lacked the necessary criteria for an adequate and well-controlled clinical trial, as reflected in the report itself. The protocol for this study showed that unsuitable patient selection reflected variable disease conditions and as a consequence, the variability of sputum volume and retention qualities precluded uniform measurement of effectiveness. No assessment of the subjective response of the patients was stated, nor was there an assurance in the protocol or results of the comparability of the different test groups of pertinent variables. In addition, the levels and methods of blinding were not documented. Although the statistical evaluation purported to show that Alevaire is more effective than either water or saline, its validity is highly questionable since Alevaire was administered to only half the number of patients who received normal saline and water, and the use of Bronkometer aerosol which in itself has mucocervant properties, unduly complicates the spirometric test. Nor does

the data obtained contain adequate detail to permit trend analysis. Another published single blind study to evaluate the comparative efficacy of Alevaire and another mucocavacant, ascumist, was conducted among 75 patients undergoing thoracic surgery. The results showed that there was no significant reduction in the viscosity of sputum with Alevaire, but that Alevaire did produce an increase of sputum volume. The investigator's statement that "both ascumist and Alevaire can increase 24-hour sputum volume" is not warranted and cannot be translated into evidence of Alevaire's effectiveness, since the study failed to provide meaningful controls in the form of water or of the drug's vehicle consisting of water, sodium bicarbonate and glycerin. Numerous other deficiencies in the design of the study cause it to fail to meet the criteria which constitute an adequate and well-controlled clinical study.

In addition to these 19 published and unpublished reports commented upon above, the citations to nine other articles were provided as evidence favorable to claims of the drug's effectiveness. No adequate and well-controlled studies, clinical or otherwise, were present. Of the nine articles, four consisted of clinical discussions of pulmonary conditions generally, two involved the concurrent use of Alevaire and other drugs, one was a study of inhalation therapy in dogs, one a preliminary report of an uncontrolled study, and one a testimonial article based on clinical impressions of Alevaire.

The Commissioner also has considered the medical documentation submitted by the petitioners and reviewed by the NAS-NRC panel, and to the materials contained in the NDA's. Again, no adequate and well-controlled clinical studies were found. Of the 21 articles reviewed and evaluated by the NAS-NRC panel, 10 were resubmitted and summarized in the Request for Hearing materials. They have been already discussed. Nine of the remaining 11 are discussions of techniques of aerosol therapy, clinical impressions or preliminary reports on Alevaire's use, or of pulmonary surface activity. In two of the articles, however, the author (Palmer) reported on two controlled clinical investigations in which the drug was compared in one with its vehicle (sodium bicarbonate, water, and glycerine), and in the other with a control solution, normal saline solution, and water. The results showed use of Alevaire to be of no advantage over the use of any of the control or comparison solution, including water.

The NDA's for Alevaire contain 33 studies or articles from the medical literature. These, too, consist only of methods and techniques of aerosol therapy, reports of animal studies, uses of the drug for conditions other than its recommended ones, clinical impressions of the drug, or in which Alevaire is mentioned only incidentally. A number were concerned with drugs other than Alevaire.

3. *Affidavits to Support the Claims of Effectiveness.* The affidavits of six physicians were submitted with the Request

for Hearing. In each of them, the affiant argues that clinical experience has shown Alevaire to be both safe and effective for its recommended uses, and each raises the argument that the criteria for adequate and well-controlled clinical studies prescribed by the regulations is impossible to meet with respect to any study of Alevaire. Neither of these two arguments raises a substantial question.

Despite the expressed opinions that the drug is both safe and effective, in only three of the affidavits (Cohen, Miller, Beck) is anything more than general clinical experience relied upon to justify such a conclusion. And in the affidavits of Cohen, Miller, and Beck, their conclusions are based on general clinical impressions and upon uncontrolled studies each has conducted on Alevaire. These studies were among those submitted in support of the Request for Hearing, and inasmuch as none meet the criteria for an adequate and well-controlled clinical study, do not constitute a valid basis for their final conclusions. And, although the conduct of an adequate and well-controlled clinical investigation of the drug may be made more difficult by conditions peculiar to its recommended use and method of administration, no valid reasons for alteration of any of the criteria has been raised.

4. *Legal Arguments.* The petitioners have urged several legal arguments in connection with the issuance of the Notice of Opportunity for Hearing. Those objections directed to the validity of the regulations clarifying the nature of the evidence to be submitted, have been resolved in *"Upjohn Co. v. Eichen,"* 422 F. 2d 914 (C.A. 6, 1970); *"Pharmaceutical Manufacturers Assn. v. Richardson,"* 318 F. Supp. 301 (D. Del., 1970); and *"Pfizer v. Richardson,"* 434 F. 2d 556 (C.A. 2, 1970). The contention that this drug is not subject to the efficacy review because it was not covered by an effective NDA on the day preceding the effective date of the 1962 Drug Amendments, is insubstantial. All drugs that were covered by new-drug applications filed at any time between 1938 and 1962 are subject to the efficacy review under the 1962 Drug Amendments. Similarly, the claimed application of different standards of evaluation by the Food and Drug Administration between Alevaire and other drugs, has no merit. The documentation of this argument in the form of an affidavit of the Medical Director of Breen Laboratories, itself points out that the two drugs are of different composition and different modes or mechanisms of action.

Therefore, the Commissioner, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (section 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds that, on the basis of new information before him with respect to Alevaire, NDA No. 10-613 and NDA No. 9-530, evaluated together with the evidence available to him when the application was approved, there is a lack of substantial evidence

that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

For the foregoing reasons, approval of new-drug applications Nos. 10-613 and 9-530, and all amendments and supplements thereto, is withdrawn effective on the date of the publication of this document.

Dated: August 27, 1971.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 71-13365 Filed 9-10-71; 8:45 am]

Office of the Secretary HEALTH SERVICES AND MENTAL HEALTH ADMINISTRATION

Statement of Organization, Functions, and Delegations of Authority

Part 3 (Health Services and Mental Health Administration) of the Statement of Organization, Functions, and Delegations of Authority for the Department of Health, Education, and Welfare (33 F.R. 15953, October 30, 1968 et seq.) is hereby amended with regard to section 3-B, Organization as follows:

Under the center head "National Center for Family Planning Services (3100)" substitute the following text:

Plans, directs, coordinates, and serves as "lead agency" for the family planning activities of the Health Services and Mental Health Administration. Specifically: (1) Develops HSMHA policy on matters pertaining to family planning activities; (2) develops long-range (5-year) family planning program objectives and plans; (3) formulates guidelines governing the preparation of annual family planning programs and reviews those programs on behalf of the Administrator; (4) administers family planning project grant and contract activities; (5) administers extramural research and training activities, both domestic and abroad (through use of Public Law 82-420 funds), incidental to family planning activities of HSMHA; (6) coordinates through Regional Offices the provision of technical assistance in family planning to State and local health organizations and to interested private organizations and institutions; (7) serves as a national clearinghouse for family planning information and data; (8) coordinates family planning activities of HSMHA with those of other operating agencies of the Department, other departments and agencies, and interested private organizations and institutions; (9) provides support and assistance to the Deputy Assistant Secretary for Population Affairs in the development of overall DHEW family planning policy and priorities, and in preparing reports to the Congress with respect to family planning program objectives, program accomplishments, and future plans; and (10) provides technical assistance and consultation to governments of other countries and public and

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its labeling and that each component of the drug contributes to the total effects claimed, and that Schering Corp. has failed to set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. No objections or documentation were presented by any other firms, and, in accordance with the provisions of 21 CFR 130.15, this failure is construed as an election by any other firm not to avail itself of the opportunity for the hearing.

The Commissioner further finds that the approval of the new drug application heretofore approved for Sigmagen (NDA 10-157) should be withdrawn on the basis of a lack of substantial evidence of effectiveness.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (§§ 505, 701, 52 Stat. 1052-1053, 1055-1056, as amended, and 76 Stat. 731-735, as amended; 21 U.S.C. 355, 371), and under authority delegated to the Commissioner (21 CFR 2.120), the request for a hearing is denied, and notice is given that the approval of the new drug application for Sigmagen tablets (NDA 10-157) and all amendments and supplements thereto is withdrawn, effective on the date of publication of this document.

Dated: March 6, 1973.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.73-4539 Filed 3-7-73; 8:45 am]

[DESI 8530; Docket No. FDC-D-141; NDA Nos. 10-613 and 8-530]

WINTHROP PRODUCTS, INC., AND
WINTHROP LABORATORIES

Alevaire; Notice of Withdrawal of Approval
of New Drug Application

In an announcement published in the FEDERAL REGISTER of July 17, 1963 (33 FR 10227), Winthrop Products, Inc., holder of new drug application No. 10-613 for Alevaire (tyloxapol 0.125 percent) and Winthrop Laboratories, Division of Sterling Drug, holder of NDA No. 8-530 for Alevaire (tyloxapol 0.125 percent), were notified of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's evaluation of the article as ineffective, and of the Food and Drug Administration's concurrence with the evaluation and its conclusions that there is a lack of substantial evidence that Alevaire will have the effect it purports and is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. Accordingly, the Commissioner of Food and Drugs noted his intent to initiate action to withdraw approval of the new drug applications for Alevaire, and invited holders of the NDAs to submit any pertinent data.

After the announcement, Winthrop met with representatives of the Food and Drug Administration on August 13, 1968, to present arguments and additional evidence in support of the claimed effectiveness of Alevaire. The arguments and data were evaluated, but failed to

provide any evidence of effectiveness derived from adequate and well-controlled clinical investigations. On December 6, 1969, there was, therefore, published in the FEDERAL REGISTER (34 FR 19399), a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of NDA's Nos. 10-613 and 8-530 for Alevaire, and all amendments and supplements thereto, on the ground that there was a lack of substantial evidence to support the claims of effectiveness for the drug for the conditions for which it is prescribed, recommended, or suggested in the labeling.

Winthrop Products, Inc., holder of NDA No. 10-613; Winthrop Laboratories, Division of Sterling Drug, Inc., holder of NDA No. 8-530; and Ereon Laboratories, Inc., a firm marketing Alevaire in the United States, filed a written appearance and request for hearing on January 20, 1970.

Submitted with the request was a statement of grounds, including the medical documentation relied upon, arguments which contended that there was an unqualified right to a hearing, and the affidavits of six physicians and scientists attesting to the drug's effectiveness. Additional medical documentation was submitted by a letter dated May 7, 1970.

On June 5, 1970, in response to the May 6, 1970, FEDERAL REGISTER publication of procedural and interpretative regulations, a supplemental election for hearing was submitted, included in which, was further medical documentation and a reiteration of the argument and reasons for a hearing as stated in the initial request for hearing. On August 13, 1970, one final medical document was submitted as a supplement to the January 20, and June 5 filings, and on March 1, 1971, the affidavit of the medical director of Ereon Laboratories was received.

On June 21, 1971, a revision of an earlier submitted study was forwarded along with five affidavits. On August 12, 1971, a submission was made containing argument and two affidavits. Finally, on January 28, 1972, petitioners made a final submission containing raw data sheets on two previously submitted studies.

On September 11, 1971, a final order was published in the FEDERAL REGISTER (37 FR 17229) denying requests for a hearing and withdrawing approval of NDA's Nos. 10-613 and 8-530 on the grounds that there is a lack of substantial evidence that the drug, Alevaire, is effective for its recommended uses.

After preparation of the order, but prior to its publication in the FEDERAL REGISTER, the data received on June 21 and August 12, 1971, as set forth above, was received and due to inadvertence, was not considered prior to publication of the final order.

On January 11, 1972, upon being advised by the Government of the inad-

vertence, the U.S. Court of Appeals for the Second Circuit set aside the order of September 11, 1971, and remanded the proceeding to the Food and Drug Administration for reconsideration of the requests of hearing in light of the data not considered.

The additional data, as well as the medical documentation reviewed by the NAS-NRC panel and the medical documentation contained in both NDAs have been considered. The Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing and that the legal arguments are insubstantial.

REASONS FOR WITHDRAWAL OF APPROVAL

1. *The drug.* Alevaire is an aqueous solution of 0.125-percent tyloxapol, 2-percent sodium bicarbonate, and 5-percent glycerin.

It is recommended in the treatment of patients "with diseases and disorders of the lungs accompanied, or complicated, by excessive or thickened bronchopulmonary secretions," and is indicated also for persons having pulmonary diseases where "the normal mechanism for elimination of secretions is diminished or absent . . . or depressed."

The rationale for Alevaire has been variously described. At the time of initial NDA approval, it was offered as a "mucolytic" detergent aerosol which exerted a liquefying effect on excessive or thickened mucous secretions, thereby aiding the patient in their expulsion. The rationale, as reflected in the labeling submitted for review by the NAS-NRC panel, is that the drug acts as a detergent aerosol facilitating the removal of the pulmonary secretions allowing for excretion by normal processes by lowering or reducing the surface and interfacial tensions and reducing their viscosity.

Alevaire is recommended for administration in an undiluted form by an aerosol nebulizer delivering a fine mist to the patient in an open tent, croup tent, or incubator. Where short periods of therapy are indicated, 10-20 ml. are recommended to be administered by a face mask, positive pressure breathing machines, or oral or nasal spray apparatus.

2. *Medical documentation.* Petitioners have presented summaries and/or copies of 19 reports and have cited nine additional articles which they contend establish Alevaire's effectiveness. The Commissioner has reviewed these submissions and concludes that they include no adequate and well-controlled studies of the type required by 21 CFR 130.12(a)(5). These studies were generally discussed in the Commission's September 11, 1971, order and are discussed individually below.

(a) *Nine cited articles.* These articles are all mentioned in the submission of January 20, 1970. These articles, except No. (8) below, all contain mere passing references to Alevaire. They are not adequate and well-controlled studies since none of them, except No. (8), involved the use of any control whatever, in violation of section 505 of the act, 21 CFR

3.66, and 21 CFR 130.12(a)(5)(ii)(a)(4). Nor is No. (8) an adequate and well-controlled study, as detailed below.

(1) S. Bloom "Case Report: Tracheostomy in Status Asthmaticus," *Annals of Allergy*, 23:532 (1965). As suggested in the title, this article is a discussion of a case history of a patient. The patient was given several drugs including Alevaire in the course of his treatment, and no mechanism was used to compare the effects of the various treatments.

(2) R. M. Cherniak "The Recognition and Management of Respiratory Insufficiency," *Anesthesiology* 25:209 (1964). As suggested in the title, this article is a discussion of respiratory insufficiency. It is not a controlled comparison of the effects of drugs.

(3) D. E. Frank "WR 1339 Inhalations in the Treatment of Asthmatic Attacks and Chronic Asthma—A Pilot Study," *Annals of Allergy* 13:313 (1955). In this test, patients suffering from an asthma attack were treated with Alevaire for 15 minutes, but Alevaire was not compared to any control.

(4) O. C. Hansen-Pruss et al., "Emphysema in the Aged," *Journal of the American Geriatric Society* 2:153 (1954). This article is a general report concerning emphysema based on the observation of 24 uncontrolled patients and contains a single unsupported statement that Alevaire is an effective expectorant.

(5) M. Joannides, Jr., "Chronic Obstructive Emphysema," *Journal of the American Medical Association* 192:105 (1965). This article, rather than studying Alevaire, discusses aspects of the treatment of emphysema by surgery. The article recommends that expectorant therapy, preferably Alevaire, be used as preoperative preparation. It is not a controlled study of Alevaire's efficacy.

(6) F. Marchetta et al., "A Method of Tracheotomy Care," *Archives of Otolaryngology* 65:296 (1957). As suggested by the title, this article is not a controlled study of Alevaire. Its only mention of Alevaire is to suggest Alevaire's administration as a method of postoperative care for tracheotomy.

(7) T. H. McGavack et al., "Metabolic Emergencies Common in the Elderly," *The West Virginia Medical Journal* 61:109 (1965). This article, rather than being a study of Alevaire, discusses metabolic emergencies commonly affecting older persons. It says, in passing, that while the various detergents and enzymes have been used to thin tenacious bronchial secretions, none has been too successful, but that Alevaire has been the most satisfactory detergent aerosol.

(8) J. H. Modell et al., "The Effects of Wetting and Antifoaming Agents on Pulmonary Surfactant," *Anesthesiology* 30:164 (1969). This study purports to compare the in vitro and in vivo effects of Alevaire (a wetting agent) and ethyl alcohol (an antifoaming agent) on normal canine pulmonary surfactant. This does not constitute adequate and well-controlled study since Alevaire was compared to ethyl alcohol, not to a proper control, i.e., Alevaire minus the active

ingredient tyloxapol. In other words, a mixture of 2 percent sodium bicarbonate, 5 percent glycerin and 93 percent water, and the test was conducted on healthy dogs, not on human patients suffering from conditions for whose treatment Alevaire is recommended.

(9) J. E. Ruben "Alevaire as an Adjuvant for Preventing Pulmonary Complications after Toracotomy (A Comparative Study of 200 Cases)," *Anesthesiology* 16:801 (1955). The title explains the subject of this article and indicates that no control was used, which is borne out by reading the article.

b. *Nineteen summarized or copied articles.* The first 14 of the articles discussed below were summarized in the submission of January 20, 1970. The other five were submitted as indicated.

1. R. Denton et al., "Mist-O-Gen Therapy and Postural Drainage for Respiratory Difficulties of the Newborn Infant: A Preliminary Report," *Journal of Pediatrics* 42:551 (1953). This article is a discussion of Mist-O-Gen—an apparatus for the administration of aerosol treatment to newborn infants suffering from respiratory difficulties. In passing, the authors suggest that the apparatus can be used to administer Triton-A-20, a former designation for tyloxapol, the active ingredient in Alevaire and one of a group of chemicals which the authors say has "proved chemically valuable." This article does not constitute an adequate and well-controlled study since it was not a comparison of Alevaire to a control as required by 21 CFR 130.13(a)(5)(ii)(a)(4).

2. B. Gans, "Acute Bronchiolitis treated with Detergent Aerosols," *Lancet* 1:1011 (1954). This article concerns the treatment of infant victims of two epidemics of bronchiolitis. During the first epidemic the mortality rate was 21.9 percent; during the second epidemic patients were treated with three detergents, including Alevaire, and none died. This is not an adequate and well-controlled study since there were no stated diagnostic criteria on the condition treated as required by 21 CFR 130.12(a)(5)(ii)(a)(2)(i) and (iii), the article did not state the method of observation and recording of results including variables measured and quantitation as required by 21 CFR 130.12(a)(5)(ii)(a)(3) and the article makes no effort to define or explain the possible effects of environmental factors. This third reason is important when one considers that the patients were in London and the first epidemic occurred between November 1952 and February 1953, dates which include the severe fog of December 5-9, 1952. The author admits that "some [patients] may well have had a more severe type of illness as a result of their exposure [to the fog]." (*Lancet* at p. 1012). Most importantly, there was no comparison of Alevaire with a control, e.g., a product containing Alevaire's components minus tyloxapol.

3. C. J. Heiberg, "Laryngitis in Children," *Southern Medical Journal* 50:383 (1957). This article discusses laryngitis in children generally, and its purpose "is to plead for teamwork early in order to

prevent anoxemia and toxemia of severe impact" (50 *Southern Medical Journal* at 383). The article mentions Alevaire as an aid in treatment of acute laryngotracheobronchitis. This article does not constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

4. M. Holmes-Siedle et al., "Acute Laryngotracheobronchitis Treated with 0.125 percent Superinone," *British Medical Journal* 2:777 (1958). This article relates to five cases of acute laryngotracheobronchitis in which Alevaire was used as part of the therapy. It is not an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

5. H. N. Kenwell et al., "Problems of Preoperative and Postoperative Cases," *American Practitioner and Digest of Treatment* 7:597 (1956). The title of this article indicates its concern. The article says that Alevaire is effective, inter alia, in liquifying bronchial secretions and should be used in preoperative and postoperative therapy in certain cases. This article merely mentions Alevaire. It is not an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

6. D. M. Little, Jr., "Fetal Salvage in Cesarean Section—The Pediatric Viewpoint," *New York State Journal of Medicine* 53:2776 (1953). This article deals with methods to lower the mortality rate of infants delivered by cesarean section especially by aiding respiration. The article, in passing, makes the statement that Alevaire has been an effective detergent. This article, containing statements about Alevaire made in passing, does not constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

7. J. B. Miller et al., "Alevaire Inhalation for Eliminating Secretions in Asthma, Sinusitis, Bronchitis and Bronchiectasis of Adults: A Preliminary Report," *Annals of Allergy* 12:611 (1954). This article makes suggestions concerning how Alevaire might be administered. In addition the article contains case reports of seventeen people with respiratory diseases and their response to treatment with Alevaire. This article is not an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4). In fact, the study itself says: "This does not pretend to be a controlled study." 12 *Annals of Allergy* at 624.

8. W. F. Miller, "Chronic Inflammatory Bronchopulmonary Disorders: A Physiologically Oriented Approach to Treatment," *Archives of Internal Medicine* 107:589 (1961). As suggested by the title, this article deals with the treatment of chronic inflammatory bronchopulmonary disorders. In passing the article says that Alevaire alleviates airway obstructions. This article, containing the living organism, the article does not

constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

9. S. P. Ravenel, "New Techniques of Humidification in Pediatrics," *Journal of the American Medical Association* 151:707 (1953). This article claims to contain the results of an in vitro experiment in which Alevaire was shown to lower the viscosity of saliva, bronchiectatic pus and amniotic fluid by 10 percent, 19 percent, and 24 percent respectively while water produced no thinning. The article also states that Alevaire has helped those with various respiratory conditions. The results of the in vitro study does not constitute an adequate and well-controlled study of Alevaire's effectiveness since in vitro tests do not assure that the same results will occur in the living organisms, the article does not explain quantitation and how variables were measured as required by 21 CFR 130.12(a)(5)(ii)(a)(3), the article does not present a summary of the methods of analysis and an evaluation of data derived from the study as required by 21 CFR 130.12(a)(5)(ii)(a)(5), and the article is conclusory and lacks detail, data and an explanation of experimental technique. In addition, Alevaire was not compared to a proper control, e.g. Alevaire minus tyloxapol.

10. M. S. Sadove et al., "Postoperative Aerosol Therapy," *Journal of the American Medical Association* 156:759 (1954). This article gives the views of the authors on the place of aerosol therapy in the care of patients after operation. The article mentions that Alevaire may be used for such therapy and offers testimonials of its effectiveness. This article does not constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

11. M. S. Segal et al., "Treatment of Chronic Pulmonary Emphysema," *American Rev. Tuberculosis* 69:915 (1954). The title of this article indicates its contents. Alevaire is mentioned as an aid in treatment. This article does not constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

12. A. Smessaert et al., "Aerosol Administration of Alevaire: II. Clinical Evaluation," *New York State Medical Journal* 55:1587 (1955). This article summarizes the reactions of 300 patients to Alevaire. The therapeutic response was listed in the article under four groups: good, appreciable, fair and poor. These responses were based on consideration of the following factors: volume, color, and viscosity of sputum or secretions; temperature and pulse; changes in the respiratory effort and in the auscultatory signs; radiologic appearance before and after therapy; and the general condition of the patient. The test found that 204 of the patients (70 percent) were in the "good" and "appreciable" category. This article does not constitute an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

13. F. C. Stiles, "Aerosol Therapy in Children," the *Wisconsin Medical Journal* 52:543 (1953). This article talks about the use of Alevaire and other aerosols for various respiratory conditions. It is not an adequate and well-controlled study since it did not compare Alevaire to a control as required by 21 CFR 130.12(a)(5)(ii)(a)(4).

14. M. L. Tainter et al., "Alevaire as a Mucolytic Agent," the *New England Journal of Medicine* 253:764 (1955). This article summarizes the conclusions of previous articles on Alevaire. The authors say that they have carried out in vitro experiments to measure surface tension effects of Alevaire on sputum. Alevaire was found to lower surface tension by 20 percent, whereas it was found that water did not lower surface tension. Other tests showed that when a glass plate was coated with Alevaire and set at a 45° angle and sputum was dropped into it, the time required for the sputum to slide a distance of 15 cm. was about one-third the time the sputum took to slide off of a glass plate which was water-wetted and held at a 45° angle. This article does not constitute an adequate and well-controlled study since in vitro results cannot be extrapolated to the living organism, the tests conducted do not show that Alevaire is effective for its recommended use since it does not show that patients with pulmonary diseases can better eliminate bronchial secretions, and it did not compare Alevaire to a proper control, e.g. Alevaire minus tyloxapol.

15. B. M. Cohen, "Ultrasonic Nebulization of Water and Mucocavacant Solutions in Patients with Obstructive Lung Disease: Volumetric and Ventilatory Responses to Acute Administration." This study was summarized in the submission of January 20, 1970, submitted as exhibit 19 of the submission of June 5, 1970 and resubmitted as revised in the submission of June 21, 1971. This test involved 15 patients with obstructive ventilatory diseases (bronchial asthma and chronic bronchitis) and retained secretions. The effects of Alevaire and distilled water were measured. The test measured several indices and concluded that Alevaire was more effective than water. This test is not an adequate and well-controlled study since the diagnostic criteria for identifying bronchial asthma and chronic bronchitis patients were not stated as required by 21 CFR 130.12(a)(5)(ii)(a)(2)(i), the method of patient selection is not explained, the study did not state the steps taken to assess subjective response and minimize bias on the part of the subject and observer as required by 21 CFR 130.12(a)(5)(ii)(a)(3), the test did not document the levels and method of blinding as required by 21 CFR 130.13(a)(5)(ii)(a)(4), and the administration of the water and Alevaire was preceded by the inhalation of a bronchodilator, meaning the effects of water and Alevaire cannot be separated from the effects of the bronchodilator. Most importantly, the

test did not compare Alevaire to a proper control, e.g. Alevaire minus tyloxapol, in other words a solution of 2 percent sodium bicarbonate, 5 percent of glycerine and 93 percent water. In addition the statistical support claimed for alevaire is not valid since the design of the experiment, although a crossover, was not analyzed as such, the baseline differences between treatment groups and patients were not adequately taken into account; nor were the summary tables submitted adequate to measure improvement for all volumetric and ventilatory responses taken, and the specific analytical model was not presented in a complete fashion. In particular, the definition of replication in the applicant's model and the magnitude of the error term and scientific degrees of freedom were not presented.

16. G. Beck, untitled and uncompleted study comparing Alevaire to isotonic saline. A description of this test was given in January 20, 1970. A summary of its progress was submitted on June 5, 1970. On June 21, 1971 Food and Drug Administration was told that Dr. Beck was having troubles finding proper patients for his study. On August 12, 1971, Food and Drug Administration was again informed of the difficulties encountered with completing this test along with Dr. Beck's affidavit concerning those difficulties. An incomplete test of this nature cannot constitute an adequate and well-controlled study since the information provided is too sketchy to evaluate.

17. W. F. Miller and P. Paez "Blind Comparison among Normal Saline, Distilled Water and Two Surface Active agents in Sputum Evacuation." This study was mentioned in the submission of January 20, 1970. A completed version was submitted as exhibit 18 of the submission of June 5, 1970. In this test 20 patients with a variety of bronchopulmonary diseases were each tested with four different substances. The test is not an adequate and well-controlled study since patient selection reflected variable disease conditions contrary to 21 CFR 130.12(a)(5)(ii)(a)(2)(i), and as a consequence the variability of sputum volume and retention qualities precluded uniform measurement of effectiveness, the test did not assure comparability in test and control groups of pertinent variables such as age, sex, severity, or duration of disease, and use of drugs other than the test drugs as required by 130.12(a)(5)(ii)(a)(2)(iii), the assessment of subjective response was not stated as required by 21 CFR 130.12(a)(5)(ii)(a)(3), an important factor in these cases where there is some question of whether patients are capable of accurate evaluation of their own sputum consistency, the study does not explain the method of observation and recording of results as required by 21 CFR 130.12(a)(5)(ii)(a)(3), the study does not explain the steps taken to minimize bias on the part of the subject and observer as required by 21 CFR 130.12(a)(5)(ii)(a)(3) and (4), the study did not provide a comparison of the results of diagnosis and treatment with a control in such a fashion as to

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permit the quantitative evaluation required by 21 CFR 130.12(a) (5) (ii) (3), and the test did not document levels and methods of blinding as required by 21 CFR 130.12(a) (5) (ii) (4). In addition the statistical analysis was not valid since Alevaire was administered to only half the number of patients who received normal saline and distilled water, the spirometric test is complicated by the use of Bronchometer aerosol which also has mucocervicant properties, and the data lack adequate detail to permit trend analysis or comprehension of methodology. Most importantly, this test is inadequate since it did not compare Alevaire to a proper control, e.g., Alevaire minus tyloxapol, in other words a solution of 2 percent sodium bicarbonate, 5 percent glycerin and 93 percent water.

18. R. E. Goldhammer et al., "Effects of a Mucocervicant on Mucus and Respiratory Tract Fluid: A Control Study in Immature Cats," *Archives of Environmental Health* 20:586 (1970). This article was mentioned in the submission of January 20, 1970, was submitted on May 7, 1970, and resubmitted as exhibit 16B of the submission of June 5, 1970. This article does not constitute an adequate and well-controlled study since there were no indications of the steps taken to minimize bias by the observer as required by 21 CFR 130.12(a) (5) (ii) (3) and (4), and cats are poor animals to use to support claims of efficacy of Alevaire in humans because the respiratory tract of a cat is short compared to the human, thereby minimizing the "fallout" of large droplets. In addition Alevaire was not compared to a proper control, e.g., Alevaire minus tyloxapol, in other words a solution of 2 percent sodium bicarbonate, 5 percent glycerine and 93 percent water.

19. J. W. Polk et al., "A Comparative Study of Alevaire and a New Mucolytic Agent, Acumist in Postoperative Patients," *The Eye, Ear, Nose and Throat Monthly* 49:30 (1970). This article was submitted on August 13, 1970, and compares Alevaire to Acumist and concludes that Acumist is a more effective mucolytic agent. This article is not an adequate and well-controlled study demonstrating Alevaire's effectiveness since it did not compare Alevaire to a proper control, e.g., Alevaire minus tyloxapol.

3. *Affidavits concerning Alevaire's effectiveness.* On January 20, 1970, petitioners submitted six affidavits which contend that clinical experience has shown Alevaire to be effective for its recommended uses and that criteria for adequate and well-controlled clinical studies prescribed by FDA regulations should be deemed inapplicable to aerosol medication.

Despite the expressed opinions that Alevaire is effective, in only four of the affidavits (Cohen, Miller, Beck, and Ravenel) is anything more than general clinical experience relied upon to justify such a conclusion. The conclusions of Cohen, Miller, Beck, and Ravenel are based on general clinical impressions and upon studies, which have not been shown to be adequate and well controlled, that

each has conducted upon Alevaire, and which therefore do not constitute a valid basis for their final conclusions.

The affidavits also argue that the regulations requiring adequate and well-controlled studies of effectiveness as a prerequisite for a hearing should not be applied to Alevaire because of the special properties of aerosol drugs. It is contended that patients cannot be properly blinded because Alevaire tastes, looks, and foams and has a consistency different than water thereby allowing the patient to recognize which preparation he is receiving. It is also said that the disease states of patients vary from day to day. These contentions do not obviate the need for compliance with the regulations. Alevaire must be compared to its own vehicle, in other words, to a product containing the ingredients of Alevaire minus tyloxapol, i.e., a solution of 2 percent sodium bicarbonate, 5 percent glycerin and 93 percent water. A patient could not detect the difference between such a compound and Alevaire. And while the severity of a disease on any given day may vary from day to day or even minute to minute, a documentation of symptom trends over a period of time could be employed so as to reduce this obstacle. An adequate and well-controlled clinical study is therefore entirely feasible.

On June 21, 1971, petitioner submitted five additional affidavits. These affidavits stated that the affiants reviewed the Miller-Paez article and the Cohen article and concluded that these articles constituted adequate and well-controlled studies as defined by FDA regulations. This conclusion can have no basis in fact and does not require a hearing since, as pointed out above, the Cohen and Miller-Paez studies do not conform to several requirements of the FDA regulations defining adequate and well-controlled studies, and, most importantly, do not even compare Alevaire to a proper control, as pointed out in the discussions of two tests, *supra*.

On August 12, 1971, petitioners submitted two additional affidavits. Both affidavits state that they have been unable to complete the studies they had agreed to perform either due to lack of personnel or a proper patient population. In addition, one concludes that there is "substantial evidence" that Alevaire is effective based, in part, on the Cohen and Miller-Paez studies. The other concludes that the Cohen and Miller-Paez studies fall within the FDA regulation for adequate and well-controlled studies. These conclusions have no basis in fact and do not require a hearing since, as pointed out above, the Cohen and Miller-Paez studies do not conform to several requirements of the FDA regulations defining adequate and well-controlled studies, and, most importantly, do not even compare Alevaire to a proper control, as pointed out in the discussions of the two tests, *supra*.

4. *Legal arguments—*a. *Alevaire is not a "grandfathered" drug.* In the submission of January 20, 1970, petitioners claimed that Alevaire is not subject to

the requirements found in the 1962 New Drug Amendments to the Federal Food, Drug, and Cosmetic Act that "new drugs" must be generally recognized as safe and effective. Petitioners base their claim of exemption on the ground that they are "grandfathered," that is that Alevaire is not a "new drug" since it falls within the exemption found in section 107(c) (4) of the 1962 Amendments, Public Law 87-781. The contention that Alevaire is not subject to the efficacy review of the 1962 Amendments to the Act is insubstantial since the drug was covered by an effective application under 21 U.S.C. 355 on the day preceding the enactment date of the 1962 Amendments and the NDA was never withdrawn or disapproved by FDA. A drug subject to an NDA prior to October 9, 1962, does not qualify for an exemption from the new drug provisions of the Act under the grandfather provisions of the 1962 New Drug Amendments. *USV Pharmaceutical Corp. v. Richardson*, 461 F. 2d 223 (C.A. 4, 1972).

b. *The right to a hearing is not unconditional.* In their submission of January 20, and June 5, 1970, petitioners contend that they have an unconditional right to a hearing concerning whether Alevaire is effective. This contention is without merit. Courts in several cases have held that there is no such unconditional right. *Diamond Laboratories, Inc. v. Richardson*, 452 F. 2d 803 (C.A. 8, 1972); *Ciba-Geigy Corp. v. Richardson*, 446 F. 2d 466 (C.A. 2, 1971); *Upjohn Co. v. Pincin*, 422 F. 2d 944 (C.A. 6, 1970); *Pharmaceutical Manufacturers Ass'n. v. Richardson*, 318 F. Supp. 301 (D. Del., 1970). These cases recognize that those petitioning for a hearing must demonstrate that they have substantial evidence of the effectiveness of their drug as evidenced by adequate and well-controlled studies. Petitioners, as pointed out above, have not presented such evidence.

5. *Summary.* Before petitioners request for hearing may be granted, the information submitted as part of the request must show there is substantial evidence that Alevaire will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling. 21 U.S.C. 355(e); 21 CFR 130.12(a) (5). Certain principles have been developed by the scientific community as essentials of adequate and well-controlled clinical investigations. They provide the basis for establishing that there is substantial evidence to support claims of effectiveness.

A well-controlled clinical investigation should provide for comparison of the results of treatment with a control which permits quantitative evaluation. The precise nature of the control must be stated and an explanation of the methods used to minimize bias on the part of observers and the analysts of the data. The level and method of "blinding" techniques must be documented.

In the case of Alevaire, a comparison of the results of use of the drug itself with an inactive preparation designed to

resemble Alevaire must be utilized. Thus, to establish effectiveness, the studies referred on would have to at least compare Alevaire to a product containing an aqueous solution of 2 percent sodium bicarbonate and 5 percent glycerin. None of the studies or articles cited make such a comparison. Moreover, the Palmer study cited by the NAS-NRC panel establishes that Alevaire containing tyloxapol, 2 percent sodium bicarbonate, and 5 percent glycerin was no more effective than the control solution containing no tyloxapol, which evidence petitioners have not refuted. Therefore, petitioners' contention is without merit.

c. *The NAS-NRC report warrants institution of withdrawal procedures.* In their submission of January 29, 1970, petitioners argue that the NAS-NRC report does not warrant the institution of withdrawal proceedings against Alevaire since, *inter alia*, the NAS-NRC panel was not familiar with the clinical use of Alevaire, the Commissioner did not conduct an independent review of Alevaire's effectiveness, and the NAS-NRC panel apparently misunderstood the true physiological effects of Alevaire. This objection is insubstantial. The NAS-NRC reviewed medical literature on Alevaire determining that it did not contain substantial evidence of its effectiveness. To the contrary, the study by Palmer, "The effect of an aerosol detergent in chronic bronchitis," *Lancet* 1:611-613 (1957), clearly established that Alevaire containing 2 detergent and sodium bicarbonate was 10 more effective than the control solution containing sodium bicarbonate but no detergent. The Commissioner conducted an independent evaluation of the NAS-NRC conclusions, the material in Alevaire's new drug application and other scientific literature relating to Alevaire. On the basis of this evaluation the Commissioner concurred that there was a lack of substantial evidence that the addition of the small amount of tyloxapol which is found in Alevaire increases the effectiveness of the product. The NAS-NRC reviewed medical literature in light of the claims for Alevaire made by petitioners. It concluded and the Commissioner concurred that there was no substantial evidence that Alevaire had its labeled physiological effects.

d. *Other arguments.* In addition to the three legal arguments discussed above, petitioners state other reasons for granting a hearing for Alevaire. None of these, however, are of any merit.

5. *Findings.* The Commissioner, on the basis of the information before him and a review of the documentation, affidavits, and legal arguments offered to support the claims of effectiveness for Alevaire, finds that there is a lack of substantial evidence that the drug has the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling, that the legal arguments are insubstantial, and that the petitioners have failed to set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic

Act (section 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under the authority delegated to the Commissioner (21 C.F.R. 2.120), the request for hearing is denied, and the approval of new drug application Nos. 10-613 and 8-539, and all amendments and supplements thereto, is withdrawn effective on the date of publication of this document.

Dated: March 2, 1973.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner
for Compliance.

[FR Doc.73-4538 Filed 3-7-73; 8:45 am]

National Institutes of Health
BREAST CANCER WORKING GROUP
Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the Breast Cancer Working Group of the Special Virus Cancer Program, March 30, 1973, at 9 a.m., National Institutes of Health, Building 31, Conference Room 7. This meeting will be open to the public from 9 a.m., March 30, 1973, to discuss the progress of the segment's program of breast cancer research during the previous 4 months and closed to the public from 9:30 a.m., March 30, 1973, in accordance with the provisions set forth in section 552(b)4 title V, United States Code and section 10(d) of Public Law 92-463. Attendance by the public will be limited to space available.

Mr. Frank Karel, Associate Director for Public Affairs, NCI, Building 31, Room 10A-31, National Institutes of Health, Bethesda, Md. 20014, 301-496-1911, will furnish summaries of the open/closed meeting and roster of committee members.

Dr. Ernest J. Plata, Executive Secretary, Building 41, Suite 300, National Institutes of Health, Bethesda, Md. 20014, 301-496-6173, will provide substantive program information.

Dated: February 23, 1973.

JOHN F. SHERMAN,
Deputy Director,
National Institutes of Health.

[FR Doc.73-4473 Filed 3-7-73; 8:45 am]

NATIONAL ADVISORY COMMISSION ON
MULTIPLE SCLEROSIS
Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the National Advisory Commission on Multiple Sclerosis on March 27, 1973, at the National Institutes of Health, Building 31, Conference Room 3. This meeting will be open to the public from 10 a.m. to 4 p.m. and will continue the investigation into the most promising avenues for research leading to causes of and preventives and treatments for multiple sclerosis. Attendance by the public will be limited to space available.

Mrs. Ruth Dudley, Information Officer, NINDS, Building 31, Room 2A03, telephone 496-5751, will furnish summaries of the meeting, rosters of the Commission members, and Dr. Harry M. Weaver, Building 31, Room 2A34, telephone 496-3523, will give Commission activities information.

Dated: February 23, 1973.

JOHN F. SHERMAN,
Deputy Director,
National Institutes of Health.
[FR Doc.73-4470 Filed 3-7-73; 8:45 am]

PERIODONTAL DISEASES ADVISORY
COMMITTEE
Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the Periodontal Diseases Advisory Committee, March 27, 1973, National Institutes of Health, Building 31-C, Conference Room 7. This meeting will be open to the public from 9:30 a.m. to 5 p.m. on March 27, to develop more specific advice to the National Institute of Dental Research in planning research strategies on periodontal disease. Attendance by the public will be limited to space available.

The Executive Secretary from whom substantive information may be obtained is Dr. Anthony A. Rizzo, Extramural Programs, National Institute of Dental Research, National Institutes of Health, Westwood Building, Room 506, Bethesda, Md. 20014.

Dated: February 23, 1973.

JOHN F. SHERMAN,
Deputy Director,
National Institutes of Health.
[FR Doc.73-4472 Filed 3-7-73; 8:45 am]

SICKLE CELL DISEASE ADVISORY
COMMITTEE
Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of the meeting of the Sickle Cell Disease Advisory Committee, March 22 and 23, 1973, National Institutes of Health, Building 31, Conference Room 4. This meeting will be open to the public from 8:30 a.m. to 5:30 p.m. on both days. The agenda items will generate discussion on subcommittee reports and program staff reports. Attendance by the public will be limited to space available.

Mr. Hugh Jackson, Information Officer, NHLI, NIH Building 31, Room 4A10, phone 496-4236, will furnish summaries of the meeting and rosters of the committee members. Substantive information may also be obtained from the Executive Secretary, Mr. Howard F. Manly, NHLI, NIH Building 31, Room 5A03, phone 496-6931.

Dated: February 28, 1973.

JOHN F. SHERMAN,
Deputy Director,
National Institutes of Health.
[FR Doc.73-4471 Filed 3-7-73; 8:45 am]

Merchant Marine Act, 1936, as amended, it should be assumed that each vessel named will engage in the trades described on a full-time basis. As stated in the prior notification, each voyage must be approved for subsidy before commencement of the voyage and the Maritime Subsidy Board will act on each request for a subsidized voyage as an administrative matter under the terms of the individual operating-differential subsidy contract. This procedure will continue throughout the 1-month extension described above.

Any person having an interest in the proposed extension of the foregoing described agreements from June 30, 1973, to July 31, 1973, and who would contest such an extension by the Maritime Subsidy Board, must, on or before June 22, 1973, notify the Board's Secretary, in writing, of his desire to intervene, with as much specificity as possible, giving those facts that the intervenor would undertake to prove at any hearing that may be ordered on the subject. Further, each such statement shall identify the contractor against which the intervention is lodged.

Dated June 13, 1973.

By order of the Maritime Subsidy Board.

JAMES S. DAWSON, Jr.,
Secretary.

[FR Doc. 73-12179 Filed 6-15-73; 8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 5530; Docket No. FDC-D-141; NDA Nos. 10-613 and 8-530]

WINTHROP PRODUCTS, INC., AND WINTHROP LABORATORIES

Alevaire; Termination of Order Withdrawing Approval of New Drug Applications

On March 6, 1973, the Food and Drug Administration published a final order in the FEDERAL REGISTER (38 FR 6305-9) denying requests for a hearing and withdrawing approval of new drug applications Nos. 10-613 and 8-530 for the drug Alevaire. On April 16, 1973, a petition for reconsideration of the order with supporting materials was filed by Sterling Drug, Inc., Winthrop Products, Inc., and Breon Laboratories. Following review of the petition for reconsideration, the Food and Drug Administration has concluded that the requests for hearing should be reevaluated.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505 (f) and (h), 52 Stat. 1052, as amended; 21 U.S.C. 355 (f) and (h)) and under authority delegated to the Commissioner (21 CFR 2.120), the order of March 6, 1973, is set aside and approval of new drug applications Nos. 10-613 and 8-530, and all amendments and supplements thereto, is reinstated.

Dated June 14, 1973.

SAM D. FINE,
Associate Commissioner for
Compliance.

[FR Doc. 73-12152 Filed 6-15-73; 8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of Interstate Land Sales Registration
[Docket No. H-73-159]

ENGLISH MOUNTAIN DEVELOPMENT, ET AL.

Notice of Hearing

Notice is hereby given that:

1. Preferred Development Corp., a Tennessee corporation and a wholly owned subsidiary of Peoples' Protective Corp., a Tennessee holding corporation, its officers and agents, hereinafter referred to as "Respondent," being subject to the provisions of the Interstate Land Sales Full Disclosure Act (Public Law 90-448) (15 U.S.C. 1701 et seq.), received a notice of proceedings and opportunity for hearing dated May 4, 1973, which was sent to the developer pursuant to 15 U.S.C. 1706(d) and 24 CFR 1710.45(b) (1), informing the developer of information obtained by the Office of Interstate Land Sales Registration showing that a change had occurred which affected material facts in the developer's statement of record for English Mountain development and the failure of the developer to amend the pertinent sections of the statement of record and property report.

2. The Respondent filed an answer received May 22, 1973, in answer to the allegations of the notice of proceedings and opportunity for a hearing.

3. In said answer the Respondent requested a hearing on the allegations contained in the notice of proceedings and opportunity for a hearing.

4. Therefore, pursuant to the provisions of 15 U.S.C. 1706(d) and 24 CFR 1720.10(b), it is hereby ordered, That a public hearing for the purpose of taking evidence on the questions set forth in the notice of proceedings and opportunity for hearing will be held before Administrative Law Judge Miles Brown, in room 7233, Department of HUD Building, 451 Seventh Street SW., Washington, D.C., on June 22, 1973, at 10 a.m.

The following time and procedure is applicable to such hearing:

All affidavits and a list of all witnesses are requested to be filed with the Hearing Clerk, HUD Building, room 10150, Washington, D.C. 20410, on or before June 21, 1973.

5. The Respondent is hereby notified that failure to appear at the above-scheduled hearing shall be deemed a default and the proceeding shall be determined against Respondent, the allegations of which shall be deemed to be true, and an order suspending the statement of record, herein identified, shall be issued pursuant to 24 CFR 1710.45 (b) (1).

This notice shall be served upon the Respondent forthwith pursuant to 24 CFR 1720.430.

By the Secretary.

Dated June 13, 1973.

George K. Bernstein,
Interstate Land Sales Administrator.
[FR Doc. 73-12098 Filed 6-15-73; 8:45 am]

ATOMIC ENERGY COMMISSION

[Dockets Nos. 50-262, 50-270, 50-287]

DUKE POWER CO.

Addendum to Final Environmental Statement

Pursuant to the National Environmental Policy Act of 1969 and the U.S. Atomic Energy Commission's regulations in appendix D to 10 CFR, part 50, notice is hereby given that the addendum to the final environmental statement prepared by the Commission's Directorate of Licensing related to the proposed issuance of operating licenses to the Duke Power Co. for the startup and operation of Oconee Units 2 and 3 is available for inspection by the public in the Commission's public document room at 1717 H Street NW., Washington, D.C., and in the Oconee County Library, 201 South Spring Street, Wallhalla, S.C. The addendum to the final environmental statement is also being made available at the Office of the Governor, State Planning and Grants Division, Wade Hampton Office Building, South Carolina 29201, and at the South Carolina Appalachian Regional Planning and Development Commission, P.O. Box 4184, 11 Regency Hills Drive, Greenville, S.C. 29608.

The "Final Environmental Statement Related to the Operation of Oconee Nuclear Station Units 1, 2, and 3" was published by the Directorate of Licensing in March 1972. Paragraph 2 of the summary and conclusions pointed out that "this statement consider the environmental impact of the simultaneous operation of all three units," although the action at the time was concerned with the proposed issuance of a license to operate unit 1.

In connection with the proposed issuance of operating licenses for units 2 and 3, the final environmental statement was reviewed and it was determined that the statement sets forth an adequate analysis and evaluation of the environmental impact of the proposed actions. Nevertheless, this addendum to the FES is issued in order to provide a progress report on the station's continuing monitoring program and to update certain "need for power" information. The information set forth in this addendum is not of sufficient importance to warrant its circulation for comment, and accordingly, the addendum is being issued as a part of the final environmental statement.

On the basis of the analysis and evaluation set forth in the final environmental statement, as supplemented by the material in this addendum, and after weighing the environmental, economic, technical, and other benefits of Oconee Nuclear Station Units 2 and 3 against environmental and other costs and considering available alternatives, it is concluded that the findings in the FES are reaffirmed; that the monitoring programs have been developed and are incorporated as part of the technical specifications for the Oconee Station; and that the further actions called for under the National Environmental Policy Act of 1969 (NEPA) and appendix D to 10 CFR, part 50, are the issuance of operating licenses for Oconee Units 2 and 3.

COMPLAINT
EXHIBIT 4
A. 26

Alevaire; Notice of Withdrawal of Approval of New Drug Applications Published in the Federal Register on August 9, 1973 (33 F.R. 21515)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION

[DESI 8530; Docket No. FDC-D-141; NDA
Nos. 8-530 and 10-613]
WINTHROP PRODUCTS, INC. AND
WINTHROP LABORATORIES

*Alevaire; Notice of withdrawal of approval
of new drug applications*

Pursuant to the proposed order withdrawing marketing approval for the drug Alevaire published in the FEDERAL REGISTER of December 6, 1969, (34 F.R. 19389), Winthrop Products, Inc., holder of New Drug Application (NDA) No. 8-530, and Winthrop Laboratories, holder of NDA No. 10-613, filed a request for a hearing on the issue of whether there was a lack of substantial evidence of effectiveness for the drug cognizable under section 505(c) of the Federal Food, Drug, and Cosmetic Act, (sec. 505(c), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)). The request for hearing was evaluated and a final decision was published in the FEDERAL REGISTER of September 11, 1971 (37 FR 17229), denying the request for a hearing and withdrawing approval of NDA's Nos. 8-530 and 10-613 on the grounds that there is a lack of substantial evidence that Alevaire is effective for its recommended uses.

The notice of withdrawal was vacated and proceedings remanded to the agency on January 11, 1972, by the United States Court of Appeals for the Second Circuit. A second notice denying the request for a hearing and withdrawing approval of the Alevaire NDAs was published in the FEDERAL REGISTER of March 8, 1973 (38 FR 6305). Thereafter, holders of the Alevaire NDAs filed a petition for recon-

COMPLAINT

EXHIBIT 4 A. 27

Alevaire; Notice of Withdrawal of Approval of New Drug Applications published in the Federal Register on August 9, 1973 (38 F.R. 21515)

sideration, and on June 14, 1973, the final order was set aside.

REQUEST FOR A HEARING

The holders of the Alevaire NDAs have submitted a large amount of documentation upon which they state the effectiveness of Alevaire has been established. All the material, including affidavits and miscellaneous citations to the medical literature, are claimed to be corroborative of the drug's effectiveness which is said to rest upon two adequate and well-controlled clinical studies of the drug denominated as the Miller-Paez study and the Cohen study. Because the Commissioner finds that the Miller-Paez and Cohen studies cannot demonstrate the effectiveness of Alevaire for its recommended uses, it is not necessary to re-analyze the other data the NDA holders cite. In any event, the Commissioner adheres to his analysis of the corroborative data in his decision of March 8, 1973.

REASONS FOR DENIAL OF HEARING AND WITHDRAWAL OF NDA APPROVAL

The claims made for Alevaire in its labeling and the manner in which the previous critiques of the Miller-Paez and Cohen studies were phrased in previous FEDERAL REGISTER notices have engendered some confusion concerning the nature of the drug and the types of clinical investigations necessary to establish drug effectiveness. Therefore, a description of the nature of Alevaire's composition in light of its labeling claims is required to place in perspective the evaluation of the Miller-Paez and Cohen studies.

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*Alevaire; Notice of Withdrawal of Approval of New Drug
Applications published in the Federal Register on
August 9, 1973 (38 F.R. 21515)*

1. *The drug.* Alevaire is a combination of three components in a sterile aqueous solution, as follows: 0.125 percent tyloxapol, with 2 percent sodium bicarbonate and 5 percent glycerin.

2. *Recommended uses.* In the Alevaire labeling printed in Physicians' Desk Reference, 25th Ed. 1971, the drug is recommended in the treatment of patients "with diseases and disorders of the lungs accompanied or complicated by the presence of excessive or thickened bronchopulmonary secretions" as may be present in, among other things, laryngotracheobronchitis and laryngitis, bronchitis and bronchiolitis, bronchial pneumonia, asthma, emphysema, allergic bronchopneumonia, neonatal asphyxia, atelectasis, diaphragmatic paralysis, bronchiectasis, pulmonary abscess and aspiration of foreign material. Alevaire is also indicated as a vehicle to which other compatible medications, such as antibiotics, may be added for administration through intermittent positive pressure breathing machines.

Alevaire is recommended for administration in an undiluted form by an aerosol nebulizer delivering a fine mist to the patient in an open tent, croup tent, incubator, etc., or by means of a face mask.

The labeled indications for use and recommended methods of administration for Alevaire have remained substantially unchanged since NDA No. 8-530 became effective in December, 1952, and NDA No. 10-613 became effective in July 1956.

3. *Rationale for Alevaire.* The labeling for Alevaire when the NDAs became effective in the mid-1950's des-

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*Alevaire; Notice of Withdrawal of Approval of New Drug
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cribed the contribution of each component in Alevaire as follows:

"The sodium bicarbonate and glycerin in Alevaire act in synergy with the detergent to create an alkaline medium for the liquefaction of mucus and to stabilize the aerosol droplets. An alkaline medium enhances the antibacterial activity of streptomycin***"

The labeling described the "Advantages of Alevaire" by stating that the addition of glycerin prevented the evaporation of aerosol droplets; that glycerin increases viscosity of the droplets causing them to remain suspended when inhaled and lost on exhalation; that the addition of a balanced amount of tyloxapol lowers the surface tension of the droplets, causing them to be deposited in the mucosa where tyloxapol liquefies mucopurulent secretions; that the addition of sodium bicarbonate to the balanced solution creates a favorable pH for the activity of tyloxapol and liquefaction of mucus; and that these effects have been demonstrated in laboratory tests. This passage in the labeling cites a paper by Miller, J. B., which contains no reference to laboratory tests. No such tests were submitted by the NDA holders as part of their request for hearing.

The Alevaire labeling printed in the Physicians' Desk Reference, 20th Ed. 1966 (and as late as 1971), described the "Action and Uses" of Alevaire as follows:

"* * * Superinone [tyloxapol] is effective in lowering surface tension; sodium bicarbonate creates an alkaline medium to help liquefy mucus; glycerin assists in the stabilization of the aerosol droplet."

However, another version of the labeling of Alevaire in circulation in 1966, and the one submitted to and reviewed

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Alevaire; Notice of Withdrawal of Approval of New Drug Applications published in the Federal Register on August 9, 1973 (38 F.R. 21515)

by the National Academy of Sciences-National Research Council, did not describe the contribution each component made to the claimed efficacy of Alevaire. It described the "Action" of Alevaire in the following terms:

"Alevaire mist lowers the surface tension and viscosity of secretions * * * whereas plain water does not * * * Alevaire loosens and frees secretions from contact with surfaces, and by greatly reducing frictional forces allows mucus to be propelled more rapidly."

This version of the labeling, unlike the labeling printed in the Physicians' Desk References, described Alevaire as a "Detergent Aerosol for Inhalation" and contained a section entitled "Tolerance" in which the toxicity of tyloxapol was described and compared with other detergents. Whether or not this labeling reflects that the NDA holders then considered tyloxapol the main ingredient is not clear, although it may be the reason why the NAS-NRC did not evaluate any ingredients in Alevaire other than tyloxapol.

Nevertheless, Alevaire is composed of a combination of ingredients whose total action is claimed to be more effective than water. The appendix to the request for hearing states that "Alevaire's action is similar to that of water, but it is more effective than water because it can be deposited further into the air passageways and because it more effectively lowers surface and interfacial tension than does water" (p. 16). Thereafter follows an abbreviated description of the function of each component in the combination and the explanation that:

"* * * the stabilized droplets of aerosolized Alevaire are able to achieve deep penetration into distal air

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Alevaire; Notice of Withdrawal of Approval of New Drug Applications published in the Federal Register on August 9, 1973 (38 F.R. 21515)

passageways, and interfacial tensions and surface tensions are reduced, thus achieving a greater mucoevacuant action than that of water." (p. 33)

The inquiry in to whether the Miller-Paez and Cohen studies demonstrate the effectiveness of Alevaire must be in terms of the claimed contribution each component makes to the drug's effectiveness (21 CFR 3.86).

4. *Clinical investigations of Alevaire.* In the petition for reconsideration filed by the NDA holders following publication of the March 8, 1973 notice, the NDA holders took issue with every facet of the evaluations of the Miller-Paez and Cohen studies contained in that notice.

The Commissioner finds that certain criticisms delineated in the petition are well-founded when the investigations are accepted at face value as is required in ruling upon the adequacy of a request for hearing under 21 CFR 130.12(a)(5) and 130.14. However, the Commission also finds that another analysis of these two studies, which would take into account the several valid objections made in the petition for reconsideration, would be a meaningless and unnecessary endeavor. Even assuming that the studies are adequate and well-controlled investigations comparing Alevaire with other control substances, a conclusion not warranted by analysis of the investigations, the studies cannot demonstrate the effectiveness of Alevaire because their design precludes assessments respecting the contribution each of the three components of Alevaire makes to the claimed effectiveness of the drug.

(a) W. F. Miller and P. Paez, "Blind Comparison among Normal Saline, Distilled Water and Two Surface Active

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*Applications published in the Federal Register on
Alevaire; Notice of Withdrawal of Approval of New Drug
August 9, 1973 (38 F.R. 21515)*

agents in Sputum Evacuation". A double-blind crossover design was used in which 20 patients with chronic bronchopulmonary diseases were randomly tested on a different aerosol solution each week for a total of three weeks. Each patient was administered distilled water and normal saline, and one half of the population was administered Alevaire and other half-Tergemist, another commercially available drug for inhalation therapy. The authors concluded that there was no difference between saline and Tergemist; that distilled water was more effective than saline; and that Alevaire was more effective than distilled water.

(b) B. M. Cohen, "Ultrasonic Nebulization of Water and Mucocervicant Solutions in Patients with Obstructive Lung Disease: Volumetric and Ventilatory Responses to Acute Administration". Fifteen patients with obstructive ventilatory diseases (bronchial asthma and chronic bronchitis) and retained secretions were administered Alevaire and distilled water aerosols in a single-blind crossover study. The study was conducted over two days, with administration of the test substances being given twice on each day. The author concludes that Alevaire was more effective than water.

Neither investigation purported to examine into the role that tyloxapol vis-a-vis sodium bicarbonate vis-a-vis glycerin plays in the claimed effectiveness of the drug. To demonstrate the claimed effectiveness of Alevaire, adequate treatment controls as required under 21 CFR 130.12(a)(5)(ii)(a)(4) are necessary i.e., a comparison of treatment groups administered Alevaire, Alevaire less tyloxapol, Alevaire less sodium bicarbonate, Alevaire less tyloxapol and sodium bicarbonate, water, etc. In this respect, the NDA holders

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in their request for hearing analyzed a study by Palmer, "The Effect of an Aerosol Detergent in Chronic Bronchitis", *Lancet* 1:611-613, 1957, (Appendix to p. 20 of request) which is a comparison in 25 patients of Alevaire to glycerine and sodium bicarbonate, and water.

The NDA holders criticize the conclusion that the study showed Alevaire is no more effective than water or saline and state that the study is really a comparison of Alevaire:

"* * * to a control aqueous solution of glycerine and sodium bicarbonate, both of which are effective additives to water for inhalation therapy. The design of this study was not adequate to elicit differences * * * between two effective mucoevacuant agents."

While each of the components is described as being "effective mucoevacuant agents", no data have been produced or cited. What is needed are data derived from adequate and well-controlled clinical investigations to show what effectiveness, if any, each of the four components of Alevaire may individually and in various combinations possess.

In any study designed to investigate each component in Alevaire insofar as it is claimed to be effective, the Commissioner is concerned that measures be incorporated to demonstrate that whatever effect is achieved is therapeutic. The Commissioner concurs with the statements of affiliates Beck, Collins, and Miller, submitted in support of the request for hearing, that water has significant irritating properties. One possible reason for water-induced irritation is that water *per se* is not a physiologic liquid. Alevaire's ingredients also are not physiological, e.g., 2 percent sodium bicarbonate content contrasts with a 1.39

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*Alevaire; Notice of Withdrawal of Approval of New Drug
Applications published in the Federal Register on
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percent physiologic value and 5 percent glycerin contrasts with a 2.6 percent physiologic value. Thus, it is possible that increases in sputum volume, if any, following administration of water, Alevaire, or other substances may reflect no more than the results of the host's response to irritants. In this frame of reference, a determination needs to be made as to which therapeutic indices would be evaluated. Also, it is possible that increased sputum volume might be a reflection not only of mucocoevacuation of retained secretions, but also of irritant-produced de novo secretions. In the latter case, a possible adverse clinical effect might accrue.

5. *Legal and other objections.* The legal objections cited in the request for hearing have been considered in the Courts and decided adversely to the NDA holders. In this respect, the Commissioner adheres to his findings published in the notice of March 8, 1973, that Alevaire is not a "grandfathered" drug; that the NDA holders must demonstrate that they are prepared to produce evidence raising genuine issues of pertinent fact to obtain a hearing; and that the NAS-NRC Report warrants institution of withdrawal procedures. The Commissioner reiterates that the other reasons cited for granting a hearing are without merit.

6. *Findings.* The Commissioner, on the basis of the information before him and a review of the documentation, affidavits and legal arguments offered to support the claims of effectiveness for Alevaire, finds that there is a lack of substantial evidence that the drug has the effect it purports or is represented to have under the conditions of use

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*Alexaire; Notice of Withdrawal of Approval of New Drug
Applications published in the Federal Register on
August 9, 1973 (38 F.R. 21515)*

prescribed, recommended, or suggested in its labeling, that the legal arguments are insubstantial, and that the petitioners have failed to set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(c), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)) and under the authority delegated to the Commissioner (21 CFR 2.120), the request for hearing is denied, and the approval of new drug applications Nos. 8-530 and 10-613, and all amendments and supplements thereto, is withdrawn effective on the date of publication of this document.

Dated: August 7, 1973.

SAM D. FINE
Sam D. Fine
Associate Commissioner for
Compliance.

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

M. A. RUBIN

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A. 36

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

Nos. 623 and 624—September Term, 1973.
(Argued February 1, 1974 Decided May 2, 1974.)
Docket Nos. 73-1628 and 73-2481

STERLING DRUG INC., WINTHROP PRODUCTS, INC.
and BREON LABORATORIES, INC.,
Petitioners,
—against—

CASPAR W. WEINBERGER, Secretary of Health,
Education and Welfare, and
ALEXANDER M. SCHMIDT, Commissioner of Food
and Drugs,
Respondents.

Before:

MULLIGAN and WATERMAN, *Circuit Judges,*
and BRYAN, *District Judge.**

Consolidated appeals seeking to set aside two orders of the Commissioner of Food and Drugs, dated March 2, 1973 and August 7, 1973, which, without a hearing, withdrew approval of new drug applications for petitioners' drug Alevaire.

* Frederick vP. Bryan, of the Southern District of New York, sitting by designation.

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Order of August 7, 1973 set aside and approval of new drug applications reinstated.

Appeal from order of March 2, 1973 dismissed as moot.

WILLIAM F. WEIGEL, New York, New York
(Rogers, Hoge and Hills, of counsel), *for*
Petitioners.

ROBERT V. ALLEN, Department of Justice, Wash-
ington, D.C. (Howard S. Epstein, Assistant
Chief, Consumer Affairs Section, Depart-
ment of Justice, on the brief), *for Respon-*
dents.

BRYAN, *District Judge:*

In these consolidated appeals, Sterling Drug Inc. and its subsidiaries Winthrop Products, Inc. and Breon Laboratories, Inc. petition to set aside two orders of the Commissioner of Food and Drugs, dated March 2, 1973 and August 7, 1973.¹ The orders, issued under the 1962 amendments to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. denied petitioners' requests for a hearing and withdrew prior approval of new drug applications for petitioners' product, Alevaire, alleging lack of substantial evidence that the drug was effective for its recommended uses.

Alevaire is an aerosol prescription drug administered to patients with chronic respiratory diseases, to aid in the evacuation of mucous from the lungs. Alevaire is a solution of 0.125% tyloxapol, 2% sodium bicarbonate, 5% glycerine, and 92.875% water. Tyloxapol is described as

¹ The appeals are taken pursuant to 21 U.S.C. § 355(h).

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the "active" muco-erucuant agent, while glycerine is a "stabilizer" and sodium bicarbonate acts to adjust the "pH factor" (alkalinity and acidity) in the lungs.

I.

Proceedings Before the FDA

Under the Federal Food, Drug and Cosmetic Act of 1938, no drug may be introduced into interstate commerce unless a New Drug Application (NDA), filed with the Food and Drug Administration (FDA), is in effect. The Act established procedures under which, after notice and hearing, the FDA could refuse to permit an NDA to go into effect or withdraw prior approval on the basis of evidence that the drug was unsafe for its intended use.

In 1962, the 1938 Act was amended to provide that the FDA could disapprove or withdraw prior approval of NDA's, not only on evidence that the drug was unsafe for intended use but also if substantial evidence is lacking that the drug is effective for its intended use. Substantially the same requirements for notice and hearing are provided.

Pursuant to the Act, as amended, the FDA undertook the review of marketed drugs, including those for which NDA's were in effect, for their therapeutic effectiveness. To aid it in this task, the FDA retained the National Academy of Sciences-National Research Council (NAS-NRC) to review the effectiveness for intended use of each approved drug.

NDA's for Alevaire had been approved by the FDA in 1952, when only the safety factor was controlling. On July 17, 1968 the FDA notified petitioners that the NAS-NRC had reported that it rated Alevaire as "ineffective"

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and that the FDA concurred in that conclusion.² Petitioners were advised that the FDA intended to institute proceedings to withdraw the approval previously given to petitioners' NDA's for Alevaire.

Pursuant to 21 U.S.C. §355(e),³ formal "Notice of Opportunity for Hearing" was given to petitioners on December 1, 1969. The notice, after reference to the NAS-NRC report, advised petitioners that the FDA proposed to issue an order withdrawing approval of the NDA's for Alevaire "on the grounds that there is a lack of substantial evidence that Alevaire has the effect which it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." It further advised petitioners of their right to avail themselves of an opportunity for a hearing and to submit clinical and investigational data to show they were entitled to a hearing.

² The NAS-NRC report stated that, "The clinical impression of the Panel is that this product is no more effective than water."

The FDA's notification included the following: "The Academy [the NAS-NRC] reports that . . . [Alevaire is] ineffective in that there is no evidence that tyloxapol . . . has any effect on secretions in the lung other than that of water in thinning secretions by simple dilution." There was no question raised as to the safety of Alevaire nor has there been at any time; only the effectiveness of the drug for intended use has been questioned.

³ 21 U.S.C. §355(e) provides, in relevant part:

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds . . .

(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

The authority in the Secretary (of Health, Education and Welfare) has been duly delegated to the Commissioner of Food and Drugs. 21 C.F.R. 2.120.

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Under the FDA regulations, 21 C.F.R. 130.14(b),⁴ a hearing can be denied only if the petitioners fail to submit at least some evidence of the drug's effectiveness stemming from adequate and well-controlled clinical investigations, 21 C.F.R. 130.12(a)(5)(ii).⁵ Petitioners duly submitted a written appearance requesting a hearing pursuant to 21 C.F.R. 130.14(b) together with a mass of evidence in support of the effectiveness of Alevaire. Petitioners' submissions as to the effectiveness of Alevaire, in addition to con-

4 21 C.F.R. 130.14(b) provides:

"If the applicant elects to avail himself of the opportunity for a hearing he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of a hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval."

5 21 C.F.R. 130.12(a)(5)(ii) attempts to define "adequate and well-controlled" studies. Several criteria are enumerated in an effort to separate those studies that are scientifically acceptable from those that are not. Only studies which meet the standards particularized in this regulation are acceptable in determining whether there is substantial evidence to support the claims of effectiveness for any drug. See *Weinberger v. Hyson, Westcott & Dunning*, 412 U.S. 609, 617-19 (1973).

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tentions that the NAS-NRC report was mistaken in major respects, relied principally on two clinical studies made by physicians whose qualifications in this field were never questioned. These studies were primarily directed at the basic criticism in the NAS-NRC report that "This product is no more effective than water". The first clinical study, by Doctors Miller and Paez (the Miller-Paez Study) concluded that Alevaire was effective as a muco-evacuant and superior to both water and saline. The other, by Dr. Cohen (the Cohen Study) compared Alevaire with water and concluded that Alevaire was a superior and effective muco-evacuant.

These studies were supported by affidavit from 10 physicians, knowledgeable and experienced in the field, that the Miller-Paez and Cohen Studies were "adequate and well-controlled" within the FDA requirements and established the effectiveness of Alevaire as a muco-evacuant.

In addition, petitioners submitted affidavits from six physicians based on their own extensive clinical experience with Alevaire to the effect that the drug was effective, and more effective than the commonly used agents of water and saline, and summaries of some 150 articles in medical and scientific literature commenting favorably on Alevaire and its use as a muco-evacuant.

On August 27, 1971, the FDA issued an order denying the petitioners' request for a hearing and withdrawing approval of petitioners' NDA's for Alevaire, primarily on the ground that the Miller-Paez and Cohen clinical studies were "not adequate and well-controlled".

The petitioners thereupon filed an appeal from the order in this Court (Docket No. 71-1898) and filed their printed briefs and appendix. At that point the FDA terminated its August 27, 1971 order and moved in this Court to remand, conceding that it had failed to consider relevant material in petitioners' submissions. It agreed to recon-

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sider petitioners' request for a hearing. The FDA's motion to remand was granted by this Court over petitioners' opposition on January 11, 1972.

A series of conferences and communications between the petitioners and the FDA ensued. On March 2, 1973, some 14 months after the petition to remand the first appeal had been granted, the FDA issued a second order again denying petitioners a hearing and withdrawing approval of the NDA's for Alevaire.

Denial of the hearing was again based upon the ground that the Miller-Paez and Cohen studies were not adequate and well-controlled under the standards of 21 C.F.R. 130.12(a)(5)(ii). For the first time, the criticism was also voiced that water was not a proper "control" with which to compare Alevaire, but that the proper "control" was Alevaire minus tyloxapol.⁶

On April 16, 1973, the petitioners requested the FDA to reconsider its March 2 order. They submitted to the FDA an extensive rebuttal of the grounds on which the order was based,⁷ which, in the light of subsequent events, was apparently well taken.

The petitioners also appealed to this Court seeking to set aside the March 2, 1973 order (Docket No. 73-1628). On June 14, 1973, when its time to file the record was about to expire, the FDA terminated its March 2 order and reinstated its approval of the NDA's for Alevaire. The order of termination stated that upon reviewing the petition for reconsideration, the FDA had concluded that the requests for a hearing should be reevaluated. The FDA

⁶ In other words, a solution of 2% sodium bicarbonate, 5% glycerine and 93% water. The FDA had previously suggested that *either* water or Alevaire minus tyloxapol would be a proper "control".

⁷ This included material supporting the suitability of the controls used in petitioners' clinical studies under 21 C.F.R. 130.12(a)(5)(ii)(a)(4)(iii).

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also moved to dismiss the pending appeal from the March 2 order. The petitioners opposed that motion, asserting they were entitled to a decision in their favor on the merits.

Then, on August 7, 1973, before the FDA's motion to dismiss the appeal from the March 2, 1973 order was argued, the FDA issued a third order denying a hearing and withdrawing approval of the petitioners' NDA's for Alevaire. This third order abandoned the grounds on which the prior two orders of March 2, 1973 and August 27, 1971 had been based. It advanced an apparently new ground for withdrawal which had never been previously raised. The ground now announced was that Alevaire was a "fixed combination" drug and that the only studies which could demonstrate its effectiveness were studies which assessed "the contribution each of the three components of Alevaire makes to the claimed effectiveness of the drug". The Miller-Paez and Cohen Studies were rejected as irrelevant to this theory.

Petitioners appealed to this Court seeking to set aside the third order of August 7, 1973 (Docket No. 73-2481). The FDA's motion to dismiss petitioners' appeal from the March 2, 1973 order was denied on November 9, 1973, and the appeal from that order was consolidated with the appeal from the subsequent August 7, 1973 order.

II.

The March 2, 1973 Order

The appeal from the March 2, 1973 order denying a hearing and withdrawing approval of the Alevaire NDA's is in a curious posture. Subsequent to the taking of the appeal, the March 2 order was terminated by the FDA's order of June 14, 1973 which granted petitioners' application for reconsideration of their requests for a hearing and reinstated approval of the Alevaire NDA's.

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The respondents' brief states: "We confessed error in that order [of March 2, 1973] before this Court on November 9, 1973 and petitioners objected. We again confess error, with the hope that petitioners will not look a gift horse in the mouth a second time."

Concededly erroneous though it was, and despite the continuing pendency of the appeal, the March 2 order is no longer in force and effect. We fail to see what relief could be granted to petitioners under these circumstances. The appeal from the March 2, 1973 order must be dismissed as moot.

III.

The August 7, 1973 Order

The questions raised on this appeal, therefore, center on the August 7, 1973 order. That order, for the first time in the lengthy and more than a little confused proceedings before the FDA characterized Alevaire as a "fixed combination drug".

The fixed combination drug classification was established on October 5, 1971 by regulation 21 C.F.R. 3.86⁸ (some three years after the Alevaire proceeding had been commenced), in pursuance of a policy formulated initially by the NAS-NRC Drug Efficacy Study of 1969.

⁸ 21 C.F.R. 3.86 provides, in relevant part:

The Food and Drug Administration's policy in administering the new-drug, antibiotic, and other regulatory provisions of the Federal Food, Drug and Cosmetic Act regarding fixed combination dosage form prescription drugs for humans is as follows:

(a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

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A fixed combination drug is one which combines "two or more drugs . . . in a single dosage form" intended for "concurrent therapy." The NAS-NRC study explained the reasons for the classification as follows:

The rating "ineffective as a fixed-combination" was brought into use to deal rationally with certain combinations of drugs, notably combinations of two or more antibiotics, one or more of which when administered alone is acknowledged to be effective for the cited indication. It is a basic principle of medical practice that more than one drug should be administered for the treatment of a given condition only if the physician is persuaded that there is substantial reason to believe that each drug will make a positive contribution to the effect he seeks. Risks of adverse drug reactions should not be multiplied unless there be overriding benefit. Moreover, each drug should be given at the dose level that may be expected to make its optimal contribution to the total effect, taking into account the status of the individual patient and any synergistic or antagonistic effects that one drug may be known to have on the safety or efficacy of the other. On these grounds, multiple therapy using fixed dose ratios determined by the manufacturer and not by the physician is, in general, poor practice.

The August 7, 1973 order withdrew approval of Alevaire upon the ground that no studies had been submitted to show that Alevaire was effective as a fixed combination drug. It rejected the Miller-Paez and Cohen Studies, about which the controversy had revolved up to that time, as irrelevant, on the ground that they did not demonstrate the effective-

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ness of Alevaire in terms of the claimed contribution each component made to the drug's effectiveness.⁹

Petitioners contend that they were entitled to notice of the specific grounds on which the FDA proposed to withdraw approval of the NDA's for Alevaire; that no notice was given them of the "fixed combination" grounds on which the August 7 order was based, and that they were therefore precluded from submitting evidence of the drug's effectiveness which would meet the criticisms expressed, for the first time, in that order. Thus, they urge, they were denied the opportunity to show that they were entitled to a hearing under the procedure provided by the statute and the FDA's own regulations.

The statute, 21 U.S.C. § 355(e), provides that "after due notice and opportunity for hearing" approval of an NDA may be withdrawn "on the basis of new information before [the FDA] with respect to such drug, evaluated together with the evidence available . . . when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented

⁹ The August, 1973 order stated, in relevant part:

In the petition for reconsideration filed by the NDA holders following publication of the March 8, 1973 notice, the NDA holders took issue with every facet of the evaluations of the Miller-Paez and Cohen studies contained in that notice.

The Commissioner finds that certain criticisms delineated in the petition are well-founded when the investigations are accepted at face value as is required in ruling upon the adequacy of a request for hearing under 21 C.F.R. 130.12(a)(5) and 130.14. However, the Commission also finds that another analysis of these two studies, which would take into account the several valid objections made in the petition for reconsideration, would be a meaningless and unnecessary endeavor. Even assuming that the studies are adequate and well-controlled investigations comparing Alevaire with other control substances, a conclusion not warranted by analysis of the investigations, the studies cannot demonstrate the effectiveness of Alevaire because their design precludes assessments respecting the contribution each of the three components of Alevaire makes to the claimed effectiveness of the drug.

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to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."¹⁰

The regulation, 21 C.F.R. 130.14(a), spells out the due notice requirement as follows: "The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner . . . to withdraw the approval of an application will specify the grounds upon which he proposes to issue his order."

On June 18, 1973, between the FDA termination of its March 2, 1973 order on June 14, 1973 and the issuance of its August 7, 1973 order, the Supreme Court decided *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609 (1973). In that case the Supreme Court held that 21 U.S.C. §355(e) and 21 C.F.R. 130.14 set up a type of summary judgment procedure in FDA administrative proceedings for the denial of NDA approval or withdrawal of such approval.

What the agency has said, then, is that it will not provide a formal hearing where it is apparent at the threshold that the applicant has not tendered any evidence which on its face meets the statutory standards as particularized by the regulations. 412 U.S. at 620.

Thus, the FDA may withdraw a drug from the market without a hearing when, and only when, "it appears conclusively from the applicant's 'pleadings' that the application cannot succeed." *Id.* at 621.

Prior to the issuance of the August 7 order, the petitioners had submitted extensive evidence of Alevaire's effectiveness as a muco-evacuant to rebut the contention in the FDA notice that Alevaire was no more effective than water. Faced with the question of whether petitioners were entitled to a hearing on that issue under the *Weinberger* standards, the FDA then shifted its grounds to the new

10 See Note 3, *supra*.

COMPLAINT
EXHIBIT 5 A. 48

fixed combination theory in its August 7 order. That order was predicated on the Notice of Opportunity for Hearing of December 1, 1969 which was the only notice ever given to petitioners. The notice, in turn, was based on the FDA announcement of July 9, 1968 stating that the FDA concurred in the report of the NAS-NRC drug efficacy study group that Alevoire was ineffective because it was "no more effective than water". While some general language was used, this was the only specific ground stated on which the FDA proposed to withdraw approval of the NDA's for the drug. It was to this ground that the Miller-Pacz and Cohen Studies and the other material submitted by the petitioners were directed.¹¹

Until August, 1973, the FDA apparently agreed that this was the issue before it. The objection to petitioners' submission raised by the FDA was that the studies were not "adequate and well-controlled". Both of the prior withdrawal orders, of August 27, 1971 and March 2, 1973, which the FDA itself terminated after they had been appealed from, were predicated on that ground.

The August 7, 1973 order was the first time the fixed combination theory had been injected into the proceedings. There was no mention of that theory as a ground for proposed withdrawal in the Notice of Opportunity for Hearing of December 1, 1969. Petitioners were never given a meaningful opportunity to submit studies or data to contravene that theory. Instead, they were arbitrarily denied the opportunity to which they were entitled to establish their right to a hearing on that ground.¹²

11 It should be noted here that the Commissioner was aware as early as August of 1968 that petitioners' studies would compare Alevoire with water, and those studies were submitted by June of 1970.

12 Withdrawal of NDA approval on the fixed combination theory has been upheld in several cases. However, in each of these cases petitioners were given notice of that theory and the opportunity to submit evidence

COMPLAINT
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The FDA argues that even if its notice to petitioners failed to specify the fixed combination theory as a ground for proposed withdrawal, nevertheless, the petitioners should somehow have inferred this and submitted evidence rebutting that theory. The FDA refers to various isolated excerpts from the record, such as general references to the labeling of Alevaire, in the December 1, 1969 Notice of Opportunity for Hearing, and the reference in its order of March 2, 1973 (which order it conceded was erroneous and withdrew) to a lack of tests comparing Alevaire to Alevaire minus its therapeutic agent tyloxapol.

In the light of this lengthy and confused record, this argument is wholly unpersuasive. What the argument amounts to is this—the petitioners should somehow have guessed whatever grounds for withdrawal the FDA might eventually come up with and therefore specification of the grounds for the proposed withdrawal required by the statute and regulation was unnecessary.

The petitioners were not required to indulge in such guesswork. They were entitled to notice of the specific grounds on which the FDA proposed to withdraw approval of the Alevaire NDA's and to an opportunity to submit evidence which would entitle them to a hearing before an order of withdrawal could be validly issued. The order of August 7, 1973 denied a hearing and withdrew approval of Alevaire without such notice to petitioners and without giving them an opportunity for such submission.¹³ Viewed in the light of the extended prior proceed-

to rebut it. *Pfizer, Inc. v. Richardson*, 434 F.2d 536 (2d Cir. 1970); *Upjohn Co. v. Finch*, 422 F.2d 944 (6th Cir. 1970); *American Cyanamid Co. v. Richardson*, 456 F.2d 509 (1st Cir. 1971). These cases serve to emphasize the importance of the notice requirement.

13 As Mr. Justice Powell said in his concurrence in *Weinberger v. Hynson, Westcott & Dunning*, *supra*:

The public interest is twofold: (i) to remove from the market, in accordance with due process, drugs of no utility or effectiveness;

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ings and the two prior orders of withdrawal without a hearing on quite different grounds, terminated by the FDA only after petitioners had appealed to this Court, it is apparent that the FDA arbitrarily disregarded the requirements of the statute and its own regulations. The order of August 7, 1973 is invalid and must be set aside and the original approval of the NDA's for Alevaire reinstated.¹⁴

A similar result was reached by the District of Columbia Circuit in *Hess & Clark v. Food and Drug Administration*, Slip Opinion 73-1581, 73-1589, D.C. Cir. Jan. 24, 1974.

Hess & Clark involved the procedures for withdrawal of approval of New Animal Drug Applications (NADA's) under 21 U.S.C. §360(b) and (c) and 21 C.F.R. 135.15 which parallel the provisions of 21 U.S.C. §355(e) and 21 C.F.R. §130.14, applicable in the case at bar. On June 21, 1972 the FDA issued a Notice of Opportunity for Hearing specifying certain tests as the grounds for proposed FDA withdrawal of NADA's for the drug diethylstilbestrol (DES) when used in the form of implanted pellets. The applicants requested a hearing and submitted evidence directed to the grounds specified in the notice. On June 27, 1973, without further notice, the FDA issued an order denying a hearing and withdrawing approval of the NADA's for DES when so used. The order was based on a new test which first came to light in April, 1973 and was quite different from the

and (ii) to retain on the market those drugs that are efficacious. In an understandable zeal to remove the former, an administrative agency must not overlook both the interest of the public and the right of the proprietor in protecting the drugs that are useful in the prevention, control or treatment of illness.

412 U.S. at 639, n. 2.

- 14 Petitioners claim that, despite the prior reinstatements of the NDA's for Alevaire, the drug has remained on an FDA "ineffective list" throughout the course of these lengthy proceedings. If this be so, we think that the present reinstatement should have the effect of removing Alevaire from such an ineffective list, as well.

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tests which had been specified as the basis for proposed withdrawal in the Notice of Opportunity for Hearing. The applicants appealed from that order. The court pointed out:

[W]here the case is governed by a statutory requirement for hearing (there being no imminent hazard to health), that hearing is not to be denied in the absence of a fair opportunity to identify material issues that require a hearing, an opportunity that embraces a suitable notice of the basis on which the agency proposes to act summarily.

It held that the FDA had not given to the DES applicant notice specifying the nature of the facts and evidence on which it proposed to withdraw NADA approval, as required by the FDA summary judgment procedures; that the applicant had thereby been deprived of the opportunity to controvert the alleged facts and present material issues which would entitle it to a hearing; and that therefore the order withdrawing approval of the NADA's for DES without a hearing was invalid. The order of withdrawal was set aside and the NADA approval which the order had attempted to withdraw was reinstated.¹⁵

In the case at bar, the August 7, 1973 order withdrawing approval of Alevaire without a hearing likewise is fatally defective.

IV.

The Adequacy of the Fixed-Combination Ground

Petitioners also contend that the record demonstrates that Alevaire is not a "fixed combination" drug and there-

¹⁵ *Cooper Laboratories, Inc. v. Commissioner, Federal Food & Drug Administration* (slip opinion 72-1866, D.C. Cir. April 19, 1974) is not germane to the notice issue presented here.

COMPLAINT

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fore not subject to the rating "ineffective as a fixed combination" applied to it by the order of August 7, 1973. Petitioners urge that this Court so hold.

While there is little in the record now before us to support the proposition that Alevaire is a fixed combination drug within the meaning of 21 C.F.R. 3.86, it is not for this Court to pass on the question on this appeal. If the FDA proposes to withdraw approval of the NDA's for Alevaire on the ground that it is ineffective as a fixed combination drug, it must follow the procedure required by the statute and regulations. It must give the petitioners notice of the specific grounds proposed for withdrawal, an opportunity to present evidence showing that they are entitled to a hearing, and a hearing if that is shown to be required. The FDA may then determine the question on a full and proper record, subject, of course, to petitioners' right of appeal to this Court from an adverse determination.

The order of August 7, 1973 is set aside and the prior approval of the New Drug Applications for Alevaire by the FDA is reinstated. The appeal from the order of March 2, 1973 is dismissed as moot.

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 8530; Docket No. FDC-D-141; NDA
Nos. 8-530 and 10-613]

ALEVAIRE

Opportunity for Hearing on Proposal To
Withdraw Approval of New Drug Appli-
cations

The National Academy of Sciences-National Research Council, Drug Efficacy Study Group evaluated the effectiveness of the drug product described below, found the drug to be less-than-effective, and submitted its report to the Commissioner of Food and Drugs. Copies of that report have previously been made publicly available and are on display at the office of the Food and Drug Administration's Hearing Clerk. After reviewing the Academy's report and the available data and information, the Commissioner concluded that the drug is less-than-effective and published his conclusion in the *FEDERAL REGISTER* of July 17, 1973 (33 FR 10277) that the drug lacks substantial evidence of effectiveness for its labeled indications.

NDA 8-530; Alevaire (a combination of 0.125 percent tyloxapol, 2 percent sodium bicarbonate, 5 percent glycerin and 92.875 percent water); Winthrop Products, Inc. (subsidiary of Sterling Drug, Inc.), 90 Park Avenue, New York, N.Y. 10016.

NDA 10-613; Alevaire (a combination of 0.125 percent tyloxapol, 2 percent sodium bicarbonate, 5 percent glycerin and 92.875 percent water); Winthrop Laboratories (subsidiary of Sterling Drug, Inc.) 90 Park Avenue, New York, N.Y. 10016.

A notice of opportunity for hearing on the proposal to withdraw approval of new drug applications Nos. 8-530 and 10-613 was published in the *FEDERAL REGISTER* on December 6, 1972 (31 FR 19389). Pursuant to that notice, Winthrop Products, Inc., holder of new drug application (NDA) No. 8-530, Winthrop Laboratories, holder of NDA 10-613, and Breen Laboratories, Inc., a firm marketing Alevaire in the United States, filed a request for hearing. The request for hearing was evaluated and an order was published in the *FEDERAL REGISTER* of September 11, 1971 (35 FR 18336), denying the request and withdrawing approval of NDAs Nos. 8-530 and 10-613 on the ground that there is a lack of substantial evidence that Alevaire is effective for its recommended uses.

In the *FEDERAL REGISTER* of February 10, 1972 (37 FR 3091), after this proceeding had been remanded to the Agency by the United States Court of Appeals for the Second Circuit, the Commissioner reinstated approval of both NDAs.

A second order denying the request for a hearing and withdrawing approval of both NDAs was published in the *FEDERAL REGISTER* of March 8, 1973 (33 FR 6365). Thereafter, holders of the NDAs filed a petition for reconsideration and in the *FEDERAL REGISTER* of June 13, 1973 (33 FR

15861), the Commissioner set aside the final order and reinstated approval of the applications.

The Commissioner reevaluated the request for hearing and, on August 8, 1973 (33 FR 21515), a third order was published in the *FEDERAL REGISTER* denying the request and withdrawing approval of both NDAs.

In consolidated appeals to the United States Court of Appeals for the Second Circuit, Sterling Drug, Inc. and its subsidiaries, Winthrop Products, Inc. and Breen Laboratories, Inc. sought judicial review of the Commissioner's orders published March 8, 1973, and August 9, 1973. On May 2, 1974, the Court set aside the order of August 9, 1973, and reinstated approval of both NDAs. It held that the notice of opportunity for hearing published December 6, 1972 was defective because it did not mention the combination drug theory as a ground for the proposed withdrawal of approval and that the firms were therefore not given a meaningful opportunity to submit studies or data to contravene that theory. The appeal from the order published March 8, 1973 was dismissed by the Court as moot. *Sterling Drug, Inc. v. Weinberger*, Nos. 73-1023 and 73-2421.

The Director of the Bureau of Drugs concludes that, in light of the foregoing, it is appropriate to issue a new notice of opportunity for hearing with respect to the drug product Alevaire. New submissions should be made in the formats and with the analyses required by 21 CFR 314.260.

The Director of the Bureau of Drugs feels that it is appropriate in this notice to point out several considerations related to demonstrating that a drug product such as Alevaire is an effective product.

Alevaire consists of water, sodium bicarbonate (to give a 2 percent aqueous solution), glycerin and tyloxapol, a detergent. It is possible to conclude that Alevaire is a combination product, with several ingredients intended to contribute to the overall claimed therapeutic effect. In fact, in its labeling the sponsor has at times indicated adherence to this interpretation. Thus, in package inserts used until 1970 the following statement appears:

Superimone [tyloxapol] is effective in lowering surface tension; sodium bicarbonate creates an alkaline medium to help liquefy mucus; glycerin assists in the stabilization of the aerosol droplet.

This statement indicates that at least the bicarbonate and tyloxapol were considered active, each playing a specific role in the overall therapeutic effect of Alevaire.

On the other hand, it is also possible to consider Alevaire as a single active component, tyloxapol, with a vehicle that happens to have some activity of its own in the treatment of patients with difficulty in mobilizing pulmonary secretions. Recent package inserts for Alevaire no longer refer to the contributions of the various components. A vehicle with therapeutic activity is, in this instance, not

a contradiction in terms. In the case of aerosols such as Alevaire, any vehicle, whether water or saline, will have activity.

Whether Alevaire is a combination or not has a bearing on the conduct and evaluation of studies to demonstrate safety and effectiveness. If it is a combination, the requirements of 21 CFR 314.111 in addition to those of 21 CFR 314.111 must be met, and the contribution to overall effectiveness of the water, bicarbonate, and tyloxapol must be assessed. This would require, at a minimum, a study including groups treated with water alone, water plus bicarbonate, water plus tyloxapol, water plus bicarbonate plus tyloxapol. (Glycerin, apparently intended to affect aerosol droplet size, could be added to all groups).

If Alevaire is a single active component in a several component vehicle, the required clinical studies are somewhat less complex. In this case evidence must be presented that Alevaire is more effective than its admittedly active vehicle. Development of such evidence would require a two-group trial: patients treated with the vehicle (water, bicarbonate, and glycerin) alone vs. patients treated with Alevaire. In this instance, a comparison of Alevaire with water or saline does not address the question of whether tyloxapol is an active drug, since any difference seen favoring Alevaire could be the result of the bicarbonate.

It is the present conclusion of the Bureau of Drugs, based in part upon the explicit labeling for Alevaire used until 1970, that Alevaire is a fixed combination drug product and that evidence of its effectiveness should be derived from adequate and well-controlled studies meeting the requirements of 21 CFR 314.111 and 21 CFR 3.86. Any request for a hearing with respect to the present notice should provide such evidence of effectiveness as a fixed combination or, alternatively, demonstrate that Alevaire is a single entity drug product and provide evidence in the form of adequate and well-controlled studies meeting the requirements of 21 CFR 314.111, that Alevaire is effective as a single entity drug product.

On the basis of all the data and the information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5) and 21 CFR 3.86, demonstrating the effectiveness of the combination drug product. The Director of the Bureau of Drugs is also unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5), demonstrating the effectiveness of Alevaire, considered as a single-entity drug product.

Therefore, notice is given to the holder(s) of the new drug application(s) and to all other interested persons that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) (or if indicated above, those parts of the application(s) providing for the drug product(s) listed above) and all amendments and supplements thereto on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

In addition to the holder(s) of the new drug application(s) specifically named above, this notice of opportunity for hearing applies to all persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice of opportunity for hearing to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (HFD-309), 5600 Fishers Lane, Rockville, Md. 20852.

In addition to the ground(s) for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug product subject to it (including identical, related, or similar drug products as defined in § 310.6) e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR 310.314), the applicant(s) and all other persons subject to this notice pursuant to 21 CFR 310.6 are hereby given an opportunity for a hearing to show why approval of the new drug application(s) should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and of all identical, related, or similar drug products.

If an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before September 12, 1974, a written notice of appearance and request for hearing, and (2) on or before October 15, 1974, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 310.14 as published and discussed in detail in the Federal Register of March 13, 1974 (39 FR 9750), recodified as 21 CFR 314.200 on March 29, 1974 (39 FR 11639).

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of any such drug product. Any such drug product may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice shall be filed in triplicate with the Hearing Clerk, Food and Drug Administration (HFD-20), Room 6-37, 5600 Fishers Lane, Rockville, Md. 20852.

All submissions pursuant to this notice, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk during regular business hours, Monday through Friday.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 52 Stat. 1052-53, as amended; 21 U.S.C. 355), and under

authority delegated to the Director of the Bureau of Drugs (21 CFR 2.121).

Dated: August 1, 1974.

J. Richard Croux,
Director, Bureau of Drugs.

[FR Doc. 74-18520 Filed 8-12-74; 8:45 am]

[DESI 734; Docket No. FDC-D-321;
NDA 734 etc.]

CERTAIN PREPARATIONS CONTAINING HISTAMINE PHOSPHATE

Follow-up Notice; and Opportunity for Hearing

In a notice (DESI 734) published in the Federal Register of August 12, 1971 (36 FR 16123), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group on Histamine Phosphate Injection containing 0.275 mg., 0.55 mg., and 2.75 mg. of histamine phosphate per ml.; Eli Lilly and Co., Post Office Box 619, Indianapolis, IN 46206 (NDA 734).

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, which is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (HFD-309), 5600 Fishers Lane, Rockville, MD 20852.

The notice of August 19, 1971, stated that:

1. Histamine phosphate injection (0.275 mg./ml.) was regarded as effective when labeled for intravenous use in the histamine test for pheochromocytoma.

2. Histamine phosphate injection (2.75 mg./ml.) was regarded as effective when labeled for subcutaneous use in the gastric histamine test.

3. The drugs were regarded as possibly effective when labeled for use in Meniere's disease; cephalalgias; and peripheral vascular diseases; and lacking substantial evidence of effectiveness of their other labeled indications.

Histamine Diphosphate Injection containing histamine phosphate 0.275 mg./ml.; Abbott Laboratories, 14th and Sherman Road, North Chicago, IL 60064 (NDA 2-854), was also included in the notice of August 19, 1971. Approval of that new drug application was withdrawn March 13, 1972 (37 FR 5711), on the grounds of failure to file certain required reports under section 505(j) of the Act (21 U.S.C. 355(j)). Final efficacy

ORDER TO SHOW CAUSE FOR PRELIMINARY INJUNCTION
A. 55

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----X

STERLING DRUG INC.,	:	74 C.V. 4282
WINTHROP PRODUCTS, INC. and	:	(LWP)
BREON LABORATORIES, INC.,	:	FOR PRELIMINARY
Plaintiffs,	:	INJUNCTION
v.	:	
CASPAR W. WEINBERGER, Secretary of	:	ORDER TO SHOW CAUSE
Health, Education and Welfare, and	:	
ALEXANDER M. SCHMIDT, Commissioner	:	
of Food and Drugs,	:	
Defendants.	:	
	:	X

-----X

Upon the affidavit of William F. Weigel, sworn to on September 30, 1974, and upon the Verified Complaint herein, and sufficient cause appearing therefor it is

ORDERED, that defendants show cause before this Court on October ¹⁰9, 1974 at 3 P.M. in Room 2703, United States Courthouse, Foley Square, New York, New York why an order should not be entered herein pursuant to Rule 65, F. R. Civ. P., enjoining defendants, their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them, during the pendency of this action from proceeding with their proposal to withdraw approval of the new-drug application for plaintiffs' product Alevaire pursuant to Notice dated August 1, 1974 and appearing at 39 Fed. Reg. 29013-29014 (August 13, 1974), on the grounds that said proceeding is

ORDER TO SHOW CAUSE A. 56

barred by the doctrines of res judicata and collateral estoppel and defendants are estopped by their own concessions and admissions from proceeding therewith, and that said proceeding is illegal and invalid under the Federal Food, Drug and Cosmetic Act, and for such other and further relief as the Court may deem just and proper; and it is further

ORDERED, that service of the moving papers and briefs upon the office of the United States Attorney for the Southern District of New York and by mail upon defendants by their counsel by 5 P.M. on ~~September~~ ^{October} 2, 1974 be deemed good and sufficient service hereof. LWA

Dated: New York, New York
~~September~~ ^{October} 1, 1974.

/s/ Lawrence A. Pierce
U.S.D.J.

AFFIDAVIT OF WILLIAM F. WEIGEL
A. 57

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----X
STERLING DRUG INC., :
WINTHROP LABORATORIES, INC. and :
BREON LABORATORIES, INC., :

Plaintiffs, :

v. :

74 Civ.

CASPAR W. WEINBERGER, Secretary of :
Health, Education and Welfare, and :
ALEXANDER M. SCHMIDT, Commissioner :
of Food and Drugs, :

Defendants. :

: AFFIDAVIT IN SUPPORT OF
: MOTION FOR PRELIMINARY
: INJUNCTION
-----X

STATE OF NEW YORK)
: SS.:
COUNTY OF NEW YORK)

WILLIAM F. WEIGEL, being duly sworn, deposes and
says:

1. I am a member of the firm of Rogers Hoge & Hills, attorneys for plaintiff herein. I make this affidavit in support of plaintiffs' motion for a preliminary injunction enjoining defendants from proceeding with a proposal to withdraw approvals of plaintiffs' new drug applications ("NDA's") for the drug Alevaire on the grounds that one part of said proposal is barred by the doctrine of res judicata and collateral estoppel from again being litigated and defendants are estopped by their prior acts and omissions from proceeding with that part of said proposal, and on the grounds that the remaining part of the proposal is barred because of its failure to comply with the

AFFIDAVIT OF W. F. WEIGEL
A. 58

statutory requirements of the Federal Food, Drug, and Cosmetic Act in 21 U.S.C. §355(e).

2. The parties hereto have recently concluded six years of administrative proceedings concerning Alevaire including three appeals to the United States Court of Appeals for the Second Circuit. These proceedings terminated in plaintiffs' favor as reflected in the decision of the Court of Appeals rendered on May 2, 1973. A copy of that decision is attached to the Complaint herein as Exhibit 5. Despite that decision, defendants have now instituted a new proceeding in which they seek, on the one hand, to raise again the exact issue which has been litigated and determined by the Court of Appeals decision, and on the other hand, to proceed alternatively on a new theory without complying with requirements of the Federal Food, Drug, and Cosmetic Act with respect to said new theory.

3. The history of this matter is set forth in detail in the decision of the Court of Appeals. Accordingly, the relevant facts will be merely summarized herein.

4. Alevaire is a prescription drug which has been available in this country and abroad since late 1952. It is a muco-evacuant agent containing as its active ingredient the detergent or surface active agent "tyloxapol" in a vehicle solution of water, sodium bicarbonate and glycerin. The drug is aerosolized and administered by inhalation to patients with chronic obstructive lung diseases accompanied or complicated by excessive or thickened broncho pulmonary secretions.

AFFIDAVIT OF W. F. WEIGEL
A. 59

5. In 1968, a panel of the National Academy of Sciences - National Research Council reviewed the effectiveness of Alevoire and concluded that there were no adequate and well-controlled investigations, as defined by the 1962 Amendments to the Federal Food and Drug Act ("the Act"), establishing the effectiveness of the drug. The text of the panel's report was as follows:

"COMMENTS: This detergent for inhalation by aerosol is marketed in a concentration of 0.125%. Thus, over 90% of the material is water. It has been shown in vitro that tyloxapol in higher concentration can affect certain physical characteristics of mucus (20). There is no evidence that the tyloxapol in this product has any effect on secretions in the lung other than that of water in thinning secretions by simple dilution (1,13,22).

"It should be noted that a number of the papers in the manufacturer's bibliography are based only on clinical impression and do not reflect adequate controls. The clinical impression of the Panel is that this product is no more effective than water."

In July 1968, the Food and Drug Administration ("FDA") sent plaintiffs a copy of the report and invited them to submit any pertinent data.

6. Plaintiffs promptly arranged for new clinical studies to be conducted to test the effectiveness of Alevoire. One study was performed by William F. Miller, M.D., Professor of Medicine at the University of Texas Southwestern Medical School and his associate, Pedro Paez, M.D., Assistant Professor of Medicine at the same institute, (the "Miller-Paez study"). Another study was performed by Burton M. Cohen, M.D.,

AFFIDAVIT OF W. F. WENGEL
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Associate Professor of Clinical Medicine at The New Jersey College of Medicine and Dentistry (the "Cohen study"). Plaintiffs informed FDA in August 1968 that these studies were underway and described the control solution being employed. (Decision of the Court of Appeals, Exhibit 5 to Complaint herein, Slip Op. p. 3133, n. 11, hereinafter "Slip Op.")

7. By June 1970, the studies were completed and submitted to FDA, along with the affidavits of 10 expert physicians attesting that the studies were "adequate and well-controlled" within the FDA requirements and established the effectiveness of Alevoire. (Slip Op. p. 3133). In August, 1971, the FDA rejected the studies as not being adequate and well-controlled and, by Notice published in the Federal Register, withdrew approval of the NDA's for Alevoire. Plaintiffs promptly appealed to the Court of Appeals and in due course printed and filed their brief and appendix. At that point, FDA admitted that it had failed to consider certain evidence which had been submitted by plaintiffs prior to the withdrawal order, and moved to remand the matter to the Agency. In January, 1972, after FDA informed the Court that it expected to conduct a prompt re-evaluation, the remand was granted, the first withdrawal order was vacated, and approval of the NDA's was reinstated.

8. Despite the assurances of a prompt re-evaluation, FDA waited over a year, until March 1973, before again issuing a withdrawal order, even though no further evidence had been submitted by plaintiffs which would require

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additional time for consideration. (Complaint, Exhibit 2).
As the Court of Appeals noted (Slip Op. p. 3127), in this second withdrawal order,

"Denial of the hearing was again based upon the ground that the Miller-Paez and Cohen studies were not adequate and well controlled under the standards of 21 C.F.R. 130.12(a)(5)(ii)."

The Court went on to point out, however, that

"For the first time, the criticism was also voiced that water was not a proper 'control' with which to compare Alevaire, but that the proper 'control' was Alevaire minus tyloxapol."⁶

Footnote 6 read:

"In other words, a solution of 2% sodium bicarbonate, 5% glycerine and 93% water. The FDA had previously suggested that either water or Alevaire minus Tyloxapol would be a proper 'control.'"

The March withdrawal order, on its face, made clear that the primary ground for rejecting the two studies was that they compared Alevaire to water and saline whereas

"Alevaire must be compared to its own vehicle, in other words, to a product containing the ingredients of Alevaire minus tyloxapol, i.e., a solution of 2 percent sodium bicarbonate, 5 percent glycerin and 93 percent water." 38 Fed. Reg. 6308. (emphasis added)

9. Plaintiffs promptly filed a Petition for Reconsideration which the Court of Appeals described as "an extensive rebuttal of the grounds on which the order was based, which, in the light of subsequent events, was apparently well taken." (Slip Op. p. 3127). As the Court noted, "This included material supporting the suitability of the controls used in petitioners' clinical studies under 21 C.F.R. 130.12(a)(5)(ii)(a)(4)(iii)." (Id., n. 7). In fact,

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plaintiffs met FDA's contention directly. They pointed out that the controls employed in the two studies were entirely appropriate under the regulations and that FDA had itself admitted in the first withdrawal order that water was a meaningful control. Donald F. Egan, M.D., Director of the Section of Pulmonary Medicine, New Britain General Hospital and author of the text, Fundamentals of Respiratory Therapy, stated in an affidavit submitted with the Petition for Reconsideration:

"The [March] order rejects the two studies on the grounds that the only proper control would be a solution consisting of 2 percent sodium bicarbonate, 5 percent of glycerine and 93 percent water. Since water and saline are two of the most commonly used mucoevacuant agents it is entirely appropriate to test the effectiveness of Alevaire against them as controls. The solution suggested by FDA as the only proper control is, in fact, merely an alternative which might have been used."

Thomas L. Petty, M.D., Associate Professor of Medicine and Head of the Division of Pulmonary Diseases at the University of Colorado School of Medicine and Medical Center, stated in an affidavit also submitted with the Petition for Reconsideration:

"I am also disturbed at the repeated comment [in the March order] that the only proper control would be a solution of 2 percent sodium bicarbonate, 5 percent glycerine and 93 percent water, that is, Alevaire minus tyloxapol. I do not agree that using this as a control is a proper study design and believe that a more inert control, such as water or saline is far more preferable."

10. FDA first informed plaintiffs that their Petition for Reconsideration would be denied, and plaintiffs

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therefore again appealed to the Court of Appeals. Then, after exclusive jurisdiction had vested in the Court pursuant to the appeal provision of the Act, Section 505(h), 21 U.S.C. §355(h), and FDA had allowed the time for transmitting the record to the Court to expire without taking any action, FDA unilaterally revoked the March order (Complaint, Exhibit 2) and moved in the Court of Appeals to dismiss the appeal therefrom. That motion was denied as the Court refused to allow FDA to again avoid judicial review. When FDA issued yet a third withdrawal order in August 1973 (Complaint, Exhibit 4), and plaintiffs appealed therefrom, the two appeals were consolidated and proceeded in due course.

11. During the course of the appeal, based on the revocation order, defendants' brief and the oral statements of defendants' counsel to the Court, it became absolutely clear that defendants had abandoned as erroneous their contention that Alevaire could only be tested against its vehicle consisting of sodium bicarbonate, glycerine and water. Instead, they rested their case solely on the ground, stated for the first time in the third withdrawal order of August 1973, that Alevaire was a fixed-combination drug within the meaning of 21 C.F.R. 3.86. According to this new theory, Alevaire's effectiveness could only be tested by comparing the effectiveness of each individual ingredient, namely, tyloxapol, water, sodium bicarbonate, and glycerine.

12. The Court of Appeals set aside the August 1973 order on the ground that plaintiffs had had no opportunity to

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respond to the newly raised fixed-combination theory. While stating that "there is little in the record now before us to support the proposition that Alevaire is a fixed-combination drug within the meaning of 21 C.F.R. 3.86," (Slip. Op. p.3137) it did not foreclose FDA from commencing a new proceeding on that ground, provided that FDA followed "the procedure required by the statute and regulations." (Id.)

13. The Court of Appeals clearly foreclosed FDA from proceeding again on the theory which formed the basis of the March 1973 order. As stated, the March order rested on the contention that the effectiveness of Alevaire could only be tested by comparing Alevaire to its vehicle, namely, Alevaire minus tyloxapol. The Court specifically found that the third order of August 1973, based on the fixed-combination theory, "abandoned the grounds on which the two prior orders of March 3, 1973 and August 27, 1971 had been based." (Slip Op. p. 3128). It noted that FDA itself had terminated the March order, "which order it conceded was erroneous," (Slip. Op. p. 3134) and that defendants herein had "confessed error" in regard to that order. (Slip. Op. p. 3129). Moreover, during oral argument of the appeals, counsel for defendants stated to the Court that FDA no longer objected to the Miller-Paez and Cohen studies as inadequate or uncontrolled, but argued only that they were unresponsive to the fixed-combination theory.

14. Despite the prior proceeding and the decision of the Court of Appeals, FDA has issued a new Notice, dated August 1, 1974 and appearing in the Federal Register

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Under Section 505(e)(3) of that Act, 21 U.S.C. §355(e)(3), a proposal to withdraw approval of a new drug application for lack of effectiveness must be based on "new information" which, evaluated together with the data available at the time the NDA was approved, indicates a lack of evidence of effectiveness.

17. In the proceedings which commenced in 1968 and terminated with the decision of the Court of Appeals last May, FDA relied on the report of the National Academy of Sciences-National Research Council as providing its "new information." The first Notice it sent to plaintiffs in July 1968 commenced as follows:

"The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group"

and continued by stating:

"The Food and Drug Administration concurs in the opinions expressed by the Academy."

A copy of this Notice is attached hereto as Exhibit 1.

18. In sharp contrast, the new Notice sets forth no "new information" as the basis for the proceeding. Indeed, as the Court of Appeals noted, defendants' fixed combination theory arose only after the Supreme Court had issued an opinion in Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609 (1973) severely limiting defendants' right to withdraw approval of NDA's without full hearings. The Court of Appeals stated:

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"On June 18, 1972, between the FDA termination of its March 2, 1973 order on June 14, 1973 and the issuance of its August 7, 1974 order, the Supreme Court decided Weinberger & Hynson, Westcott & Dunning, 412 U.S. 609 (1973).

* * *

"Prior to the issuance of the August 7 order, the petitioners had submitted extensive evidence of Alevaire's effectiveness as a muco-evacuant to rebut the contention in the FDA notice that Alevaire was no more effective than water. Faced with the question of whether petitioners were entitled to a hearing on that issue under the Weinberger standards, the FDA then shifted its grounds to the new fixed combination theory in its August 7 order." (Slip Op. pp. 3132-3133)

We submit that no "new information" exists and that the fixed combination theory was a last minute fiction designed to avoid the impact of the Supreme Court's decision. In the absence of a showing of such "new information" as required by the Act, defendants have no statutory basis for proceeding pursuant to their new Notice on the fixed combination theory.

19. Plaintiffs have been severely damaged by the long pendency of the prior proceeding, despite the fact that it terminated ultimately in their favor. As a result of FDA's numerous public notices, adverse publicity and FDA's maintenance of Alevaire on defendants' widely circulated list of "ineffective" drugs, 41 C.F.R. §3-1.352 et seq., which prohibits purchase of Alevaire by federal agencies, sales of Alevaire have dropped approximately 63% since 1968. The maintenance of a new proceeding, challenging anew and improperly the validity of the Miller-Paez and Cohen studies and raising, without proper basis, the untenable fixed combination theory, will further and irreparably damage the

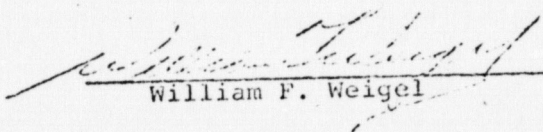
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drug and its makers. In addition, of course, plaintiffs will be put to the time and expense of responding to an invalid proposal.

20. I also wish to point out, as the Court of Appeals noted, that "There was no question raised as to the safety of Alevaire nor has there been at any time; only the effectiveness of the drug for intended use has been questioned." (Slip Op. p. 3124). Thus, the granting of preliminary relief will in no way jeopardize the public interest.

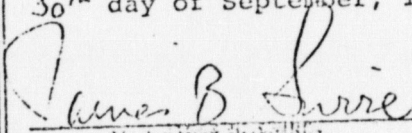
21. Plaintiffs are moving by order to show cause because a full response to defendants' new proposal is due by October 15, 1974, and defendants have refused to extend the time for such response.

22. No prior request for the relief requested herein has been made.


William F. Weigel

Sworn to before me this

30th day of September, 1974.


NOTARY PUBLIC
State of New York
No. 51-2015050
Qualified in New York County
Expires March 30, 1975

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Exhibit 2

MUCOLYTIC AEROSOL PREPARATIONS CONTAINING TYLOXAPOL OR
SODIUM ETHASULFATE

*Drugs for Human Use, Drug Efficacy Study Implementation
Announcement*

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

1. Alevaire (tyloxapol 0.125 percent); Winthrop Products, Inc., 90 Park Avenue, New York, N. Y. 10016.
2. Alevaire (tyloxapol 0.125 percent); Winthrop Laboratories, Division of Sterling Drug, 90 Park Avenue, New York, N. Y. 10016.
3. Tergemist (sodium ethasulfate 0.125 percent; potassium iodide 0.1 percent); Abbott Laboratories, 14th and Sheridan Road, North Chicago, Ill. 60064.

The Academy reports state that these articles are ineffective in that there is no evidence that tyloxapol or sodium ethasulfate in the amount present in these preparations has any effect on secretions in the lung other than that of water in thinning secretions by simple dilution. Further, the concentration of potassium iodide in the Tergemist preparation is too low to contribute to the claimed effectiveness of the drug.

The Food and Drug Administration concurs in the opinions expressed by the Academy and concludes that there is a lack of substantial evidence that either Alevaire or Tergemist will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

Accordingly, the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the new-drug applications for Alevaire and Tergemist.

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Exhibit 2

Prior to initiating such action, however, the Commissioner invites the holders of the new-drug applications for Alevaire and Tergemist, as well as any person who may be adversely affected by removal of these drugs from the market, to submit any pertinent data bearing on the proposal within 30 days from the date of publication of this announcement in the FEDERAL REGISTER. Any such data should be addressed to the Special Assistant for Drug Efficacy Study Implementation, Bureau of Medicine, Food and Drug Administration, 200 "C" Street SW., Washington, D. C. 20204.

This announcement is made to give persons who may be adversely affected by withdrawal of the drugs from the market notice of the proposed action based on the evaluation of these articles.

The holders of the new-drug applications for these drugs have been mailed a copy of the NAS-NRC report. Any other interested person may obtain a copy of the NAS-NRC reports on Alevaire or Tergemist by writing to the Food and Drug Administration, Press Relations Office, 200 "C" Street SW., Washington, D. C. 20204.

This notice is issued pursuant to the authority vested in the Secretary of Health, Education, and Welfare, by the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and delegated to the Commissioner (21 CFR 2.120).

Dated: July 9, 1968.

HERBERT L. LEY, JR.,
Commissioner of Food and Drugs.

[F.R. Doc. 68-8494; Filed, July 16, 1968; 8:51 a.m.]

AFFIDAVIT OF W. F. WEIGEL
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AFFIDAVIT OF SERVICE

STATE OF NEW YORK)
 : SS.:
COUNTY OF NEW YORK)

EDGAR FARRAN, being duly sworn, deposes and
says:

I am over 18 years of age, am not a party to
this action and reside at 160-56 26th Avenue, Flushing,
New York, New York 11358. On October 1, 1974, I served
the annexed Order to Show Cause For Preliminary Injunction,
Affidavit of William F. Weigel, Summons and Complaint
and Plaintiffs' Memorandum in Support of Motion for Pre-
liminary Injunction upon:

1. The office of the United States Attorney for
the Southern District of New York by de-
livering personally true copies thereof to
one of the attorneys in said office; and
2. Howard Epstein; Esq., attorney for defendants,
at Consumer Affairs Section, Antitrust
Division, United States Department of Justice,
Washington, D. C. 20530, the address
designated by said attorney for that purpose,
by depositing true copies of same enclosed
in a postpaid properly addressed wrapper, in a
post office or official depository under the
exclusive care and custody of the United
States Post Office Department within the State
of New York.

Sworn to before me this
1st day of October, 1974.

Anne Santino
Notary Public

Edgar Farran
Edgar Farran

ANNE SANTINO
Notary Public, State of New York
No. 41-8761685
Qualified in Queens County
Cert. Filed in New York County
Commission Expires March 30, 1976

[illegible]

Plaintiffs, :

v. _____ :

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INTRODUCTION

We proceed on two grounds. First, that defendants are barred by the doctrines of res judicata and/or collateral estoppel and are estopped by their prior concessions and admissions from proceeding to withdraw

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approval of the NDA's for plaintiffs' drug Alevaire on the theory that proof of effectiveness must be demonstrated by comparing Alevaire to its vehicle (water, sodium bicarbonate, and glycerine). Second, that defendants are barred by Section 505(e)(3) of the Federal Food, Drug and Cosmetic Act ("the Act"), 21 U.S.C. §355(e)(3), from proceeding to withdraw approval of the NDA's for Alevaire on the theory that it is a fixed-combination drug for which proper evidence of effectiveness is lacking, in that defendants lack the "new information" required by the aforesaid statute before they may institute and maintain such a proceeding.

STATEMENT OF FACTS

The history of the Food and Drug Administration's ("FDA's") evaluation of the drug Alevaire stretches over a six-year period and forms a bizarre patchwork of administrative and regulatory arbitrariness in the critical area of public health. That history now includes no less than four attempts by the FDA to withdraw approval of the NDA's for Alevaire, three separate appeals to the United States Court of Appeals for the Second Circuit, and three reinstatements

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of approval of the NDA's for Alevaire after the FDA's attempted withdrawals had been shown to be unsupportable. That history is set forth in some detail in the May 2, 1974 decision of the United States Court of Appeals for the Second Circuit, reinstating approval of the NDA's for Alevaire, (Complaint, Exhibit 5), and in the affidavit of William F. Weigel, submitted in support of the motion for preliminary injunction herein. We summarize below the facts relevant to this motion.

The NDA's for Alevaire were first approved by the FDA in 1952 and since then Alevaire has been widely prescribed in this country and abroad for use in chronic obstructive lung diseases to aid in the evacuation of broncho pulmonary secretions. Alevaire consists of an active ingredient, the detergent or surface active agent, tyloxapol, in a vehicle solution of water, sodium bicarbonate and glycerine.

The First Withdrawal Order

In 1966, the FDA commissioned the National Academy of Sciences - National Research Council ("NAS-NRC") to review all drugs, such as Alevaire, whose NDA's had been approved prior to 1962, to determine whether there was adequate proof of effectiveness as defined in the 1962 amendments to the Act.* In 1968, the NAS-NRC panel which reviewed Alevaire

*The role of the NAS-NRC is discussed in Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 614 (1973). See also, Pfizer, Inc. v. Richardson, 434 F.2d 536, 539 (2nd Cir. 1970).

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found that, evaluated pursuant to the new requirement for evidence of effectiveness under the 1962 amendments, there was a lack of evidence that the active ingredient in Alevair, tyloxapol, was any more effective than water in thinning secretions in the lung.* The FDA first published a notice of the results of the NAS-NRC review of Alevaire and its concurrence with those results in the Federal Register in July 1968, and by notice dated December 1, 1969, issued a proposal to withdraw approval of the NDA's for Alevaire.

In response to the NAS-NRC review and the FDA's notices based thereon, plaintiffs submitted to the FDA evidence confirming the effectiveness of Alevaire including two new studies (by Miller-Paez and Cohen) which had been undertaken to meet the doubts raised by the NAS-NRC

*The text of the NAS-NRC panel's comments is as follows:

"COMMENTS: This detergent for inhalation by aerosol is marketed in a concentration of 0.125%. Thus, over 90% of the material is water. It has been shown in vitro that tyloxapol in higher concentration can affect certain physical characteristics of mucus (20). There is no evidence that the tyloxapol in this product has any effect on secretions in the lung other than that of water in thinning secretions by simple dilution (1,13,22).

"It should be noted that a number of the papers in the manufacturer's bibliography are based only on clinical impressions and do not reflect adequate controls. The clinical impression of the Panel is that this product is no more effective than water."

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report and FDA's concurrence therein. Plaintiffs also submitted the sworn statements of ten experts in the field that in their expert opinion the new clinical studies concerning Alevaire were adequate and well-controlled and demonstrated the effectiveness of Alevaire and its superiority to the control test solutions, water and saline.

FDA subsequently issued an order dated August 27, 1971*in which it stated its conclusion that the studies submitted by plaintiffs were not adequate and well-controlled and withdrew approval of the NDA's without granting plaintiffs a hearing. After plaintiffs had appealed the withdrawal order to the United States Court of Appeals for the Second Circuit, the Agency confessed that it had failed to consider all the data submitted by plaintiffs and requested the Court of Appeals to remand the matter to the Agency for further consideration. In anticipation of a prompt re-evaluation, this motion was granted and the NDA's for Alevaire were reinstated.

The Second Withdrawal Order

After taking over a year to review the evidence it had overlooked, the FDA issued a second withdrawal order dated March 2, 1973, (Complaint, Exhibit 2) denying plaintiffs a hearing and again declaring the Miller-Paez and Cohen studies

*Complaint, Exhibit 1.

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to be inadequate and uncontrolled. This time, however, FDA shifted its grounds for criticizing the studies. In its 1971 order, FDA had quarreled with the methodology of the studies but had accepted the nature of the control solutions used in the studies. One study, the Miller-Paez study, had compared Alevaire to both water and saline solutions. The Cohen study had compared Alevaire to water.* In its second withdrawal order, however, FDA's principal contention was that Alevaire must be compared to its vehicle, namely, a solution of sodium bicarbonate, glycerine, and water.

Plaintiffs filed a Petition for Reconsideration, supported by the sworn statements of recognized experts in the field that while the control suggested by FDA might be suitable, those used in plaintiff's studies were equally valid if not preferable, and were clearly permissible under FDA's own regulations, 21 C.F.R. 130.12(a)(5)(ii)(a)(4), (now recodified at 21 C.F.R. 314.111(a)(5)(ii)(a)(4)). FDA first notified plaintiffs that the Petition for Reconsideration would be denied. Then, after plaintiffs had appealed the second withdrawal order to the Court of Appeals, FDA acknowledged the

*These control solutions had been chosen because they were the two most commonly used alternate mucoevacuant solutions, and because the NAS-NRC review panel itself and FDA's Notice concurring therein had compared Alevaire to water. FDA's first withdrawal order had acknowledged the suitability of the controls utilized by plaintiff's studies and, as the Court of Appeals has noted, defendants were "aware as early as August of 1968" of the nature of the controls to be employed. (Slip. Op. p. 3133, fn.11).

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validity of the criticisms made in the Petition for Reconsideration, revoked the second withdrawal notice, and reinstated approval of the NDA's (Complaint, Exhibit 3). Simultaneously, it moved in the Court of Appeals to dismiss plaintiffs' appeal.

Since exclusive jurisdiction had already vested in the Court of Appeals pursuant to Section 505(h) of the Act, 21 U.S.C. §355(h), and to prevent FDA from again avoiding judicial review of its actions, that Court denied defendants' motion to dismiss the appeal.

The Third Withdrawal Order

In August 1973, FDA issued a totally new withdrawal order based on the theory, raised there for the first time, that Alevaire was a fixed-combination drug within the meaning of 21 C.F.R. 3.86. (Complaint, Exhibit 4). Plaintiffs appealed to the Court of Appeals from this order as well, and the Court promptly ordered consolidation of the appeals.

Decision of the Court of Appeals

In May, 1974, the Court of Appeals issued its decision. (Complaint, Exhibit 5). Based on the revocation order, the August 1973 withdrawal order, defendants' briefs, and on statements made by defendants' counsel during oral argument, the Court found that FDA had conceded error in its

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March 1973 order and had abandoned the grounds for withdrawal of approval of the NDA's asserted therein. Since the March order had already been revoked by FDA, however, the Court found that the relief sought by plaintiffs had already been achieved and thus dismissed their appeal from that order as moot.

With respect to the August 1973 order, the Court stated that it found little in the record to support the FDA's new assertion that Alevaire was a fixed-combination drug and dismissed FDA's order on the grounds that the Agency arbitrarily had violated the law and its own regulation in failing to give plaintiffs notice or opportunity to respond to the eleventh-hour assertion that Alevaire was a fixed-combination drug. The Court emphasized that any proceeding based on the fixed-combination theory would have to be in accordance with the requirements of the Act and the regulations promulgated by FDA thereunder. The Court also decided that FDA should remove Alevaire from a government-prepared and circulated list of drugs the NAS-NRC had found ineffective.*

The New Withdrawal Proposal

On August 13, 1974, defendants caused to be

*FDA has refused to do so, and there is pending in the Court of Appeals a motion by plaintiffs to compel the FDA to comply with the Court's decision in that respect.

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published in the Federal Register a fourth, new Notice of Proposal to Withdraw Approval of New Drug Applications for Alevaire, 39 Fed. Reg. 29013-29014. (Complaint, Exhibit 6) Continuing their arbitrary and inconsistent conduct of the six years of the prior proceedings, defendants, in their new Notice, attempt to revive an issue specifically abandoned by them as erroneous. Implicitly recognizing the impropriety of such action, they also seek to proceed, in the alternative, on the theory that Alevaire may be a fixed-combination drug. Thus, the Notice states:

"It is possible to conclude that Alevaire is a combination product, with several ingredients intended to contribute to the overall claimed therapeutic effect.

* * *

"On the other hand, it is also possible to consider Alevaire as a single active component, tyloxapol, with a vehicle that happens to have some activity of its own in the treatment of patients with difficulty in mobilizing pulmonary secretions.

* * *

"It is the present conclusion of the Bureau of Drugs ... that Alevaire is a fixed combination drug product and that evidence of its effectiveness should be derived from adequate and well-controlled studies meeting the requirements of 21 C.F.R. 314.111 and 21 C.F.R. 3.86. Any request for a hearing with respect to the present notice should provide such

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evidence of effectiveness as a fixed combination ... "(Emphasis added)

The Notice goes on to say, however, that plaintiffs may

"alternatively, demonstrate that Alevaire is a single entity drug product and provide evidence in the form of adequate and well-controlled studies meeting the requirements of 21 CFR 314.111 that Alevaire is effective as a single entity drug product."

It is this fourth proposal which plaintiffs contend is unlawful and improper and concerning which they seek injunctive relief herein.

ARGUMENT

Introduction

It is apparent that defendants' new Notice, insofar as it considers Alevaire to be a single-entity drug, is barred by the decision of the Court of Appeals and the concessions and admissions made by defendants in the prior proceeding. In their new Notice, defendants again contend, as they did in their March, 1973 order, that Alevaire must be compared to its own vehicle. Thus, the new Notice states:

"If Alevaire is a single active component in a several component vehicle, the required clinical studies are somewhat less complex. In this case evidence must be presented that Alevaire is more effective than its admittedly active vehicle. Development of such evidence would require a two-group trial: patients treated with the vehicle (water, bicarbonate,

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and glycerin) alone vs. patients treated with Alevaire."

This is precisely the proposal which was included in FDA's second withdrawal order in March 1973, rebutted by plaintiffs' Petition for Reconsideration and by the sworn statements of independent experts in the field submitted to FDA by plaintiffs, and abandoned by FDA in its third notice of withdrawal in August 1973 and in its briefs and argument before the Court of Appeals.

Plaintiffs maintain that Alevaire is a single entity drug, the effectiveness of which was established in the prior proceedings by the Miller Pacz and Cohen studies and the other substantial evidence presented by them. We here contend that defendants may not be allowed to relitigate the validity of the evidence proving Alevaire's effectiveness as a single entity drug since that precise evidence was at issue and determined in plaintiffs' favor in the prior proceedings.

Insofar as defendants would now proceed on the proposition that Alevaire may be a fixed-combination drug, defendants are barred for lack of the "new information" required by statute, Section 505(e)(3), 21 U.S.C. §355(e)(3), and in the absence of such information, defendants may

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not proceed with their withdrawal proposal.

- I. The Defendants' Proposal to Withdraw Approval of Plaintiffs' New Drug Applications, Insofar as it is Based on a Requirement That Plaintiffs Test Alevaire Against Its Vehicle, Is Barred Under the Doctrines of Res Judicata and Collateral Estoppel

As stated, the new Notice requires that Alevaire be tested against its vehicle, namely, sodium bicarbonate, glycerine and water, before it can be established to be effective as a single-entity drug. This is precisely the ground raised in the March 1973 order wherein, as the Court of Appeals noted,

"[T]he criticism was also voiced that water was not a proper 'control' with which to compare Alevaire, but that the proper 'control' was Alevaire minus tyloxapol.⁶

⁶In other words, a solution of 2% sodium bicarbonate, 5% glycerine and 93% water. The FDA had previously suggested that either water or Alevaire minus tyloxapol would be a proper 'control'." (Slip. Op. p. 3127)

This is the exact contention that the Court of Appeals found to have been "abandoned" and "conceded [to be] erroneous." (Slip Op. p. 3128, 3134).

Surely there must come an end to defendants' efforts to continue to raise issues which have previously been determined. The Supreme Court in United States vs.

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Utah Construction and Mining Co., 384 U.S. 394, 422 (1966)

stated:

"When an administrative agency is acting in a judicial capacity and resolves disputed issues of fact before it which the parties have had an adequate opportunity to litigate, the courts have not hesitated to apply res judicata to enforce repose."

It is, of course, the fundamental and long-established purpose of the doctrines of res judicata and collateral estoppel to insure repose.

"The general principle announced in numerous cases is that a right, question, or fact distinctly put in issue and directly determined by a court of competent jurisdiction ... cannot be disputed in a subsequent suit between the same parties or their privies; and even if the second suit is for a different cause of action, the right, question, or fact once so determined must, as between the same parties or their privies, be taken as conclusively established, so long as the judgment in the first suit remains unmodified." Southern Pacific R. Co. v. United States, 168 U.S. 1, 48-49 (1897)

Whether the present proceeding by defendants against plaintiffs be viewed as the same or a different cause of action as the previous proceeding is relevant only insofar as it determines whether the principle applied be denominated technically as res judicata or collateral estoppel. The effect of the principle is the same since whether by res judicata or collateral estoppel, defendants

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are barred from again attempting to proceed against plaintiffs on the basis that Alevaire must be compared to its vehicle.

"[W]here the second action between the same parties is upon a different cause or demand, the principle of res judicata is applied much more narrowly ... Since the cause of action involved in the second proceeding is not swallowed by the judgment in the prior suit, the parties are free to litigate points which were not at issue in the first proceeding ... But matters which were actually litigated and determined in the first proceeding cannot later be relitigated. Once a party has fought out a matter in litigation with the other party, he cannot later renew that duel. In this sense, res judicata is usually and more accurately referred to as estoppel by judgment, or collateral estoppel. Commissioner v. Sunnen, 333 U.S. 591, 597-98 (1948)

Here defendants have not only had the opportunity to litigate the issue, but have themselves raised the issue and then specifically and formally abandoned it after plaintiffs made a full and "well taken" response thereto. (Slip. Op. p. 3127). After six years and three appeals, the attempt to renew this issue constitutes harassment by defendants which should not be countenanced by this Court.

Since the issue was before the Agency and the Court of Appeals, and since the decision of the Court of

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Appeals makes clear that said issue has been concluded in plaintiffs' favor, defendants are estopped from attempting again to raise this issue. Tait v. Western Maryland R. Co., 289 U.S. 620(1933); Commissioner of Internal Revenue v. Western Union Tel. Co., 141 F.2d 774 (2nd Cir. 1944), cert. denied 322 U.S. 751(1944). Also applicable is United States v. Willard Tablet Co., 141 F.2d 141 (7th Cir. 1944) where the doctrine of res judicata was applied to an attempt by FDA to relitigate an issue of fact that had previously been adjudicated between the government and respondents, even though the government in the earlier proceeding was a different Federal agency, the Federal Trade Commission. Thus, res judicata certainly applies here where the FDA itself is the agency involved in both proceedings.

The principles of res judicata and collateral estoppel have been applied against the government in a variety of situations. See Vestal v. Commissioner of Internal Revenue, 152 F.2d 132 (D.C. Cir. 1945); Chapman v. El Paso Natural Gas Co., 204 F.2d 46 (D.C. Cir. 1953); Nager Electric Co. v. United States, 396 F.2d 977 (Ct. Cl. 1968)

In Vestal, supra at 136-137, the court held:

"[T]he Commissioner, having made, within the scope of his authority, with full knowledge of all the facts and being fully conscious of the problem involved, an election to collect a tax upon a given transaction upon a stated

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basis, cannot later be heard to assert another tax upon the same transaction ..."

Similarly, defendants here have also, with full knowledge of the facts and being fully conscious of the problem involved, made an election to abandon the contention that Alevaire should be tested against its vehicle. Thus they cannot now assert that contention again.

II. The Defendants' New Withdrawal Proposal, Insofar as it is Based on a Requirement that Plaintiffs Test Alevaire Against its Vehicle, is Also Barred By Defendants' Previous Admissions and Concessions

In addition to the doctrines of res judicata and collateral estoppel, defendants are also estopped from proceeding anew on the previously raised theory since they formally and specifically, in orders, briefs and on oral argument of counsel, abandoned said contention and conceded it to be erroneous.

There are numerous cases which hold that once a party, including the government, concedes a fact or an issue in the course of a proceeding, it will be bound by the concession. Cover v. Schwartz, 133 F.2d 541 (2nd Cir. 1942); cert. denied 319 U.S. 748 (1943).

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Fenix v. Finch, 436 F.2d 831 (8th Cir. 1971); United States v. Commanding Officer, 446 F.2d 124 (8th Cir. 1971); United States v. Star Construction Co., 186 F.2d 666 (10th Cir. 1951).

This Court should, therefore, enjoin defendants from again seeking to litigate the issue of whether Alevaire must be tested in comparison with its vehicle solution of water, sodium bicarbonate, and glycerine, since that issue was raised and then abandoned by defendants in the prior proceedings concluded by the Court of Appeals decision on May 2, 1974.

III. Defendants Are Barred from Proceeding Against Alevaire on the Grounds That It is a Fixed Combination Drug Within the Meaning of 21 C.F.R. 3.86 Since Defendants Have Failed to Meet the Jurisdictional Requirement of "New Information" Upon Which to Base Such a Proceeding as Required by Section 505(e) (3) of 21 U.S.C. §355(e) (3)

One having received a license from a governmental agency is entitled to the lawful use of his rights thereunder. Thus, while such rights are not irrevocable, the government may not arbitrarily or without statutory foundation withdraw such license.

Approval of an NDA is, in effect, the grant of a license to market a drug. And Congress has provided that

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such approval may not be withdrawn willy-nilly without adequate reason. Thus, before the FDA can proceed to withdraw approval of an NDA based on lack of effectiveness, Section 505(e)(3) of the Act, 21 U.S.C. §3. requires as a condition precedent that the Agency have new information which, evaluated together with the data available when the NDA was approved, indicates that there is a lack of evidence of effectiveness.

The language of the statute is as follows:

"(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds ... (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof ..."
(Emphasis added)

We submit that the new Notice states no "new information" as required by the Act to support the proposition that "it is possible to conclude that Alevaire is a combination product" and that, in fact, defendants possess no such requisite information.

We note that despite FDA's withdrawal order of August, 1973 (Complaint, Exhibit 4) which was based exclusively

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on the ground that Alevaire was a fixed-combination drug,
the Court of Appeals noted:

"[T]here is little in the record now
before us to support the proposition
that Alevaire is a fixed combination
drug within the meaning of 21 C.F.R.
3.86 ..."

(Slip Op. p. 3137)

Indeed, the Court was apparently suspicious of the circum-
stances which gave rise to the new theory, suggesting that
it was an eleventh-hour attempt to avoid the impact of a
Supreme Court decision. As the Court stated:

"On June 18, 1973, between the FDA
termination of its March 2, 1973
order on June 14, 1973 and the
issuance of its August 7, 1973 order,
the Supreme Court decided Weinberger v.
Hynson, Westcott & Dunning, 412 U.S.609
(1973).

* * *

"Prior to the issuance of the August
7 order, the petitioners had sub-
mitted extensive evidence of Alevaire's
effectiveness as a muco-evacuant to rebut
the contention in the FDA notice that
Alevaire was no more effective than
water. Faced with the question of
whether petitioners were entitled to a
hearing on that issue under the Weinberger
standards, the FDA then shifted its
grounds to the new fixed combination
theory in its August 7 order." (Slip
Op. pp. 3132-3133)

We share that suspicion and suggest that under
such dubious circumstances, defendants should, at the least,

*The Court apparently anticipated that any new proposal
would be based on additional information not in the prior
record. But the new Notice is conspicuously lacking in any
such new evidence.

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be required to show that they meet the statutory requirements before they may force plaintiffs to submit to another withdrawal proceeding.

In the proceedings against Alevaire which commenced in 1968, FDA relied on the report of the NAS-NRC panel as providing its "new information." The first Notice FDA sent to plaintiffs in July 1968 commenced as follows:

"The Food and Drug Administration has evaluated reports received from the National Academy of Sciences - National Research Council, Drug Efficacy Study Group ..."

and continued

"The Food and Drug Administration concurs in the opinions expressed by the Academy ..."

A copy of that Notice is attached as Exhibit 1 to the Weigel affidavit.

We did not then, and do not here, challenge the sufficiency of such reports to serve as the requisite "new information." Obviously, defendants themselves rely on such reports to meet the requirement of "new information" in proceedings implementing the NAS-NRC drug efficacy review of pre-1962 drugs. In the preamble to FDA's recently revised

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hearing regulations, FDA discussed the NAS-NRC review of new drugs approved prior to the 1962 amendments. The preamble stated:

"The Commissioner notes that, for all drugs subject to the NAS-NRC review, this [review] constitutes the first evaluation by the Food and Drug Administration for effectiveness. Thus, a determination of lack of proof of effectiveness does not necessarily result from evaluation of new data or information. Instead, it results from an evaluation of all existing effectiveness data or information, for the first time, and a determination that it fails to include the type of evidence of effectiveness required by the statute and regulations. The courts have consistently recognized that this evaluation [the NAS-NRC review and FDA acceptance thereof] is sufficient to constitute the 'new evidence' required by the statute, on the basis of which the determination of a lack of substantial evidence may properly be made. Once the drug effectiveness study project is completed, of course, and all new drugs have been reviewed for both safety and effectiveness, this situation will no longer arise."
39 Fed. Reg. at 9752 (Emphasis added)

While the NAS-NRC report on Alevaire may have justified institution of the 1968 proceedings, it can in no way support the new fixed-combination proposal. It is apparent that the NAS-NRC review panel considered Alevaire to be a single entity drug with tyloxapol as that entity and, in fact, the report makes no mention of the phrase "fixed combination." (See fn. p. 4 supra , for the Panel report)

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Moreover, the NAS-NRC report on Alevaire has been merged into and is barred by the termination of the proceedings which began in 1968. Also, as defendants themselves acknowledge "once the drug effectiveness study project is completed," as it has now been with respect to Alevaire, the "situation will no longer arise" where the NAS-NRC review and FDA's concurrence therein would constitute the statutorily required new information.

In order now to proceed to withdraw approval of the NDA's for Alevaire on the grounds that it is ineffective as a fixed combination, defendants must have "new information" that Alevaire is a fixed combination drug within the meaning of 21 C.F.R. 3.86. We submit there is nothing in the current Notice or in the prior record, which constitutes such basis. Lacking such basis, the proceeding may not continue and defendants should be enjoined from proceeding to withdraw approval of plaintiffs' NDA's under the fixed combination theory.

IV. A Preliminary Injunction Should Issue
Since Plaintiffs Are Likely to Prevail
on the Merits and Will Suffer Irreparable
Harm if the Proceeding Goes Forward, and
the Public Interest Will Not be Harmed
by an Injunction

As the Court of Appeals held in Gulf & Western Industries, Inc. v. Great Atlantic & Pacific Tea Co., Inc.,

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476 F.2d 687, 692 (2nd Cir. 1973),

"the two-fold requirement for a preliminary injunction is a demonstration of probability of success on the merits and a showing that irreparable harm will result if such relief is denied."

The facts and arguments presented above, we believe, clearly demonstrate that defendants are proceeding illegally against plaintiffs, on the one hand by requiring plaintiffs to relitigate an issue already adjudicated in plaintiffs' favor, and on the other hand, by proceeding on the fixed-combination theory in the total absence of the statutorily required "new information" to support that theory. In this regard, it is significant that the Court of Appeals has strongly indicated that defendants' fixed combination theory is without merit (Slip. Op. p. 3137). It is thus apparent that plaintiffs, in seeking a preliminary injunction, have satisfied their burden of showing a likelihood of success.

While plaintiffs' likelihood of success on the merits is clear, it should be noted that "the burden [of showing probable success] is less where the balance of hardships tips decidedly toward the party requesting the temporary relief," Dino De Laurentiis Cinematografica, S.p.A. v. D-150, Inc., 366 F.2d 373, 375 (2nd Cir. 1966).

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That is unquestionably the case here. First, it is evident that defendants will suffer absolutely no hardship from the issuance of a preliminary injunction here. They have previously themselves caused substantial delay in the evaluation of Alevaire. Plaintiffs' evidence was submitted in June 1970 yet defendants took until August 1971 before issuing their first withdrawal order. After that order was revoked, defendants took over a year to evaluate seven affidavits totalling less than 20 pages of text.

Second, it is unquestioned that there is absolutely no issue as to the safety of Alevaire. As the Court of Appeals stated in its May 2, 1974 decision, "There was no question raised as to the safety of Alevaire nor has there been at any time; only the effectiveness of the drug for intended use has been questioned." (Slip Op. p. 3124, n. 2) Nor has any question of safety been raised in the new Notice. Thus, the granting of preliminary relief will in no way jeopardize the public interest. Indeed, it would help protect the public interest "to retain on the market those drugs that are efficacious ... [A]n administrative agency must not overlook both the interest of the public and the right of the proprietor in protecting the drugs that are

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useful in the prevention, control or treatment of illness." Weinberger v. Hynson, Westcott & Dunning, supra at 639, n. 2 (Powell, J., concurring).

In contrast with the total lack of harm to defendants or the public interest in granting the preliminary injunction, the harm to plaintiffs from a denial of the injunction would be substantial and irreparable. Plaintiffs have been severely damaged by the protracted prior proceedings which terminated with the Court of Appeals decision of May 2, 1974. As a result of FDA's numerous public notices, adverse publicity, and the maintenance of Alevaire on defendants' widely circulated list of "ineffective" drugs, which prohibits purchase of Alevaire by government agencies, 41 C.F.R. §3-1.352 et seq.,* sales of Alevaire have declined approximately 63% since 1968 (Weigel Aff. ¶19).

The Supreme Court has acknowledged that plaintiffs are part of a "sensitive industry in which public confidence in their drug products is especially important." Abbott Laboratories v. Gardner, 387 U.S. 136, 153 (1967). The courts have further recognized that pharmaceutical sales, once lost, are difficult if not impossible to recapture

*As would be expected, state and local agencies often follow the federal lead and private physicians and institutions are reluctant to purchase drugs branded as "ineffective" by FDA.

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"because of a permanent loss of medical confidence and a permanent loss of sales to competing products." American Home Products Corp. v. Finch, 303 F. Supp. 448, 452 (D. Del. 1969). It is obvious that plaintiffs' drug product Alevaire is rapidly approaching the point where it will no longer be commercially viable as a result of the protracted and repeated harassment by defendants and their inconsistent theories, scientifically invalid criticisms, and arbitrary and capricious denial of due process to plaintiffs.

In addition, plaintiffs should not be forced to expend the time and expense of participation in an illegal and improper agency action. The attempt of defendants to relitigate an issue foreclosed against them constitutes a serious violation of due process of law guaranteed to plaintiffs by the Fifth Amendment, and in itself makes this case a proper one for preliminary injunctive relief against the agency. Fay v. Douds, 172 F.2d 720 (2nd Cir. 1949).

As Moore points out, the

"Bad faith, if any, of the party seeking relitigation, difficulties imposed by a subsequent suit or suits on the party seeking an injunction, in the expense of time, money and energy required to defend, and the effect of continued litigation on his business or reputation, are considered by courts

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when asked to enjoin relitigation of matters previously adjudged."1B Moore's Federal Practice ¶0.408[2], at 957-58, and cases cited therein.

All these factors are present here and call for injunction of the agency proceeding.

It is also clearly recognized that agency action which is contrary to the agency's governing statute should be enjoined. Leedom v. Kyne, 358 U.S. 184 (1958).

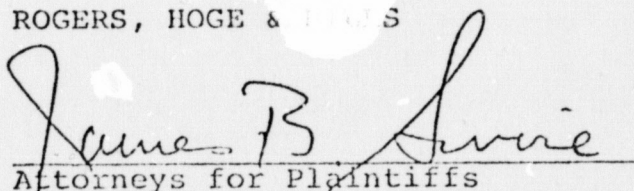
CONCLUSION

For the reasons stated above, a preliminary injunction should issue enjoining defendants from proceeding with their proposal of August 1, 1974, pending final judgment herein.

Dated: New York, New York
September 30, 1974

Respectfully submitted,

ROGERS, HOGE & SWIRE


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JS:par

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

STERLING DRUG INC., WINN-DIXIE
PHARMACEUTICALS, INC. and ELI LILLY
LABORATORIES, INC.

Plaintiffs:

74 Civ. 4232 (LHP)

-v-

CAROL W. BERNHARDT, Secretary
of Health, Education and Welfare,
and ALFRED H. SCHWARTZ,
Commissioner of Food and Drugs,

Defendants.

DEFENDANT'S MEMORANDUM IN OPPOSITION
TO GRANT OF A PRELIMINARY INJUNCTION

INTRODUCTION

The manufacturers and distributors of the drug Alevaize have brought this action to enjoin the Commissioner of Food and Drugs ("the Commissioner") from proceeding to withdraw approval of the new drug application ("NDA") now in effect for Alevaize. Alevaize is an aerosol prescription drug administered to patients with chronic respiratory diseases to clear mucous from the lungs. Defendants have stated their intent to withdraw approval of Alevaize by publication

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JS:par

of notice in the Federal Register of August 13, 1974
(39 Fed. Reg. 29013-29014)

In this proceeding, by affidavit, and if necessary, by the presentation of testimony, the Government will demonstrate that, contrary to the claims made by plaintiffs, in proceeding to withdraw approval of the Alovarsine NSA, the Food and Drug Administration has complied with both the procedures set forth in the Federal Food, Drug, and Cosmetic Act of 1938, as amended, 21 U.S.C. §301 et seq. and the applicable regulations promulgated thereunder as well as with the ^{opinion} of the United States Court of Appeals for the Second Circuit in Wyething Drug, Inc. v. Weinberger, slip op. nos. 623 and 624, May 2, 1974 (See Pl. Ex. 5). Rather, the present proceeding by plaintiffs will be shown to constitute a final and desperate effort to forestall the removal from the market by the Commissioner of a product which the Food and Drug Administration has determined to be ineffective, but which has been and continues to be sold to the public with FDA approval.

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~~THE SECRETARY AND ADVISORY COMMITTEE~~

JS:par

Under the Food and Drug Act as originally enacted in 1938, the FDA could only disapprove or withdraw approval of a drug if it determined that the drug was unsafe for its intended use. In 1962, Congress amended the Act to require further that all drugs on the market be proven effective for their intended use. Under 21 U.S. §355(e) Congress provided that:

The Secretary shall, after due notice and opportunity for a hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds . . . (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. . . .

As used in §355(e), the term "substantial evidence" is defined by §355(d) to mean:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that

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the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or approved in the labeling or proposed labeling thereof.

The 1962 Amendments thus presented the FDA with an enormous task of reviewing the efficacy of all new drugs that had been cleared only for safety between 1938 and 1962. In 1966, a contract with the National Academy of Sciences - National Research Council was signed whereby the NAS-NRC was to review the efficacy of all such drugs. The FDA then published orders in the Federal Register requiring the drug manufacturers to submit certain information regarding each approved drug, including references to evaluations of the effectiveness of the drug. The purpose was to permit the manufacturers of opportunity to identify the best available evidence which they believed supported the claims made for the drug. NAS-NRC began submitting its first reports on October 11, 1967, and submitted the last report on April 15, 1969. In January, 1968, the FDA began implementation of the NAS-NRC reports. The procedure adopted has been to evaluate each report and to release it to the public only after the FDA evaluation.

JP:pm

regulation, requires any applicant who desires hearing to submit reasons:

"Why the application . . . should not be withdrawn, the applicant with a well-organized and well-documented analysis of the clinical and other data, and all data he is prepared to submit in support of his application to the agency of regulatory law. . . . When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact . . . , O. C., no adequate and well-controlled clinical investigations to support the claims of effectiveness,"

The Commissioner may deny a hearing and enter an order withdrawing the application based solely on these data.

21 C.F.R. §130.14(b).

This "summary judgment-type procedure has been scrutinized by the courts and repeatedly sustained. As Judge Friendly wrote in Pfizer, Inc. v. Richardson, 434 F.2d 536, 543 (CA 2 1970)

"While the controversy over a particular drug raises an issue of 'adjudicative facts' [cite omitted] we perceive no denial of due process in Congress' directing an agency that it need not accord a trial-type hearing unless the affected party shows in advance that there is something substantial to hear."

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JS:par

More recently, the Supreme Court itself in Wainwright v. Hornum, 412 U.S. 602, 619-621 (1973) explicitly approved of this procedure. As the Court observed:

We cannot impute to Congress the design of requiring, nor does due process demand, a hearing when it appears conclusively from the applicant's "pleadings" that the application cannot succeed. [Footnote omitted].

The NAS-NRC panels evaluated approximately 16,500 claims made on behalf of the 4,000 drugs marketed pursuant to effective NDA's in 1962. Seventy percent of these claims were found not to be supported by substantial evidence of effectiveness, and only 424 drugs were found effective for all their claimed uses. If FDA were required automatically to hold a hearing for each product whose efficacy was questioned by the NAS-NRC study, even though many hearings would be an exercise in futility, we have no doubt that it could not fulfill its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act.

If this were a case involving trial by jury as provided in the Seventh Amendment, there would be sharper limitations on the use of summary judgment, as our decisions reveal. [Cites omitted] But Congress surely has great leeway in setting

standards for releasing on the public, drugs which may well be miracles or, on the other hand, merely easy money-making schemes through use of fraudulent articles labelled in mysterious scientific dress. The standard of "well-controlled investigations" particularized by the Regulations is a protective measure designed to ferret out those drugs for which there is no affirmative reliable evidence of effectiveness. The drug manufacturers have full and perfect notice of the evidence they must present to obtain approval and under these circumstances we find FDA hearing regulations unexceptionable on any statutory or constitutional ground. (emphasis added)

It is the use of this procedure which the Commissioner has most recently invoked against the drug Alevaire and which plaintiffs here seek to enjoin.

STATEMENT OF FACTS

New Drug Applications for Alevaire were approved by the FDA in 1952 when only the safety of the drug had to be demonstrated. In 1968, the NAS-NRC study conducted on Alevaire as part of the FDA's general efficacy review found that there was a lack of evidence that the active ingredient in Alevaire, tyloxapol, was any more effective than water in thinning secretions in the lung. After publishing a notice of the results of that study, the FDA issued a notice in the Federal Register on December 6,

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1969 (34 F.R. 19389) of its intent to withdraw approval of the NDA's for Alevaire "on the grounds that there is a lack of substantial evidence that Alevaire has the effect which it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labelling thereof." Petitioners thereupon requested a hearing and submitted among others, the so-called Miller-Pacz and Cohen studies as well as the sworn statements of ten experts concerning the tests. On August 27, 1971, the FDA issued an order denying a hearing and withdrawing approval of the NDA's for Alevaire, principally on the ground that the studies submitted were "not adequate and well-controlled." (36 Fed. Reg. 18336) Of the 19 reports submitted in all, the FDA found that twelve involved nothing more than discussions of clinical impressions and observations. The remaining reports were described and their defects noted.

When plaintiffs appealed to the Court of Appeals, the FDA requested and the Court of Appeals

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agreed, to remand the matter to the agency for further review. The reason for the decision by the agency was its realization that a revised study submitted by plaintiffs on June 21, 1971 and a submission by them with affidavits filed on August 12, 1971, had inadvertently not been considered prior to the decision denying a hearing and withdrawing approval.

Following reconsideration of the entire record the FDA issued a second withdrawal order on March 2, 1973, (38 Fed. Reg. 6305) on the grounds that the materials submitted included "no adequate and well-controlled studies of the type required by 21CFR § 130.12(c)(8)." In the notice the agency went through the studies individually and detailed its objections to each one. Specific criticism was directed at the Miller-Paez and Cohen studies on the grounds that water was not a proper control with which to compare Alevaire, but that the proper control was Alevaire minus its claimed active ingredient, tyloxapol, i.e. a solution of 2% sodium bicarbonate, 5% glycerine and 93% water.

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Plaintiffs thereupon submitted extensive rebuttal evidence to the agency, requested reconsideration and simultaneously appealed its decision. The FDA on June 14, 1973 granted the petition for reconsideration, terminated its withdrawal order, and moved to dismiss the appeal. (38 Fed. Reg. 15861)[Pl. Ex. 3] Prior to any decision on the motion by the Court of Appeals, the agency issued a third withdrawal order and denied a hearing. This order, issued on August 7, 1973 (38 Fed. Reg. 21515) [Pl. Ex. 4] was in fact the agency's decision following reconsideration of the request for a hearing. In explaining the grounds for its decision, however, the agency noted:

Even assuming that the studies are adequate and well-controlled investigations comparing Alevaire with other control substances, a conclusion not warranted by analysis of the investigations, the studies cannot demonstrate the effectiveness of Alevaire because their design precludes assessments respecting the contribution of each of the three components of Alevaire makes to the claimed effectiveness of the drug."

The agency thus considered Alevaire to be a fixed combination drug, meaning a different type of experimentation was required to prove efficacy.

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This classification was not established until October 5, 1971 by regulation 21 C.F.R. 326, some three years after the Alcazar proceedings had commenced.

[See Sterling Drug. v. Weinberger at note 8]

Plaintiffs appealed that order as well and when the Court of Appeals denied the agency's motion to dismiss the appeal of the March order, the two cases were consolidated.

In its opinion, the Court of Appeals dismissed the appeal from the March 2 order as moot since the order was admittedly erroneously issued and was now moot in any event. The Court then addressed itself to the August 7th order. What the Court ultimately held was that the agency had acted improperly in denying a hearing and withdrawing approval of the NDA in the August 7th order on the grounds that plaintiffs had failed to submit evidence to show the drug to be an effective fixed-combination drug when all prior notices of intent to withdraw approval had been directed at the fact that the studies were not "adequate and well-controlled." In other words, the FDA had acted improperly in issuing a notice of intent to withdraw approval on the single-

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entity theory and then, after all the various procedural twists, actually denying a hearing and withdrawing the drug on grounds that no studies had been submitted to show that Alevalaire was effective as a fixed combination drug. In sum, plaintiffs had not been given notice of the theory on which the FDA was actually withdrawing approval of Alevalaire nor an opportunity to submit evidence to rebut that theory prior to the actual withdrawal of approval on August 7. The Court noted in conclusion that:

They were entitled to notice of the specific grounds on which the FDA proposed to withdraw approval of the Alevalaire NDA's and to an opportunity to submit evidence which would entitle them to a hearing before an order of withdrawal could be validly issued. The order of August 7, 1973 denied a hearing and withdrew approval of Alevalaire without such notice to petitioners and without giving them an opportunity for such submission.

The Court then indicated that if the agency wished to proceed on this new theory it must give plaintiffs notice of its intent to withdraw the drug, the specific grounds on which it proposed to do so, and an opportunity to submit evidence and obtain a hearing thereupon. Accordingly, on August 13, 1974,

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the agency published in the Federal Register a notice of intent to withdraw approval of Alevaine, apprising plaintiffs of the specific grounds for so doing, and affording them an opportunity to request a hearing and to submit evidence in support of the drug's effectiveness in support of their request.

(39 Fed. Reg. 29812) [Def. Ex. 1]. On August 15, 1974, plaintiffs sought to postpone the time to file until 30 days after the Court of Appeals acted on a motion which is still pending before it. [Def. Ex. 2].

This request was denied in a letter dated August 29, 1974 [Def. Ex. 3]. Pursuant to an order issued by Judge Bryant in American Public Health Ass'n. v. Veneman, 349 F. Supp. 1311 (D.D.C. 1972) [The order is attached as Def. Ex. 4], the agency is barred from issuing such extensions in any case. Accordingly, on September 10, plaintiffs formally requested a hearing [Def. Ex. 5]. To this date, however, no evidence to support this request, as is required by the applicable regulations, 21 CFR 314.200, has been submitted, and if none is forthcoming the agency will deny the request for a hearing and withdraw approval of

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Alevaire on October 15th, as per its notice of August 13.

Faced with the prospect of this action, the plaintiffs then sought to circumvent the agency procedures by bringing this action for a preliminary injunction on October 1, 1974.

ARGUMENT

It is important to understand precisely that which plaintiffs claim here for they do not contend either that the agency has failed to comply with the requisite procedures or that Alevaire is in any way exempted therefrom. In the notice of intent to withdraw approval of August 13, 1974, the agency has attempted to be as candid and fair as possible in dealing with plaintiffs product. The notice acknowledges that:

It is possible to conclude that Alevaire is a combination product, with several ingredients intended to contribute to the overall claimed therapeutic effect...it is also possible to consider Alevaire as a single active component, tyloxapol, with a vehicle that happens to have some activity of its own.

After thus candidly expressing the two possible characterizations, the notice described the different

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types of studies which would be required to demonstrate effectiveness under either theory.*

*Whether Alevaire is a combination or not has a bearing on the conduct and evaluation of studies to demonstrate safety and effectiveness. If it is a combination, the requirements of 21 CFR 314.111 in addition to those of 21 CFR 314.111 must be met, and the contribution to overall effectiveness of the water, bicarbonate, and tyloxapol must be assessed. This would require, at a minimum, a study including groups treated with water alone, water plus bicarbonate, water plus tyloxapol, water plus bicarbonate plus tyloxapol. (Glycerin, apparently intended to affect aerosol droplet size, could be added to all groups).

If Alevaire is a single active component in a several component vehicle, the required clinical studies are somewhat less complex. In this case evidence must be presented that Alevaire is more effective than its admittedly active vehicle. Development of such evidence would require a two-group trial: patients treated with the vehicle (water, bicarbonate, and glycerin) alone vs. patients treated with Alevaire. In this instance, a comparison of Alevaire with water or saline does not address the question of whether tyloxapol is an active drug, since any difference seen favoring Alevaire could be the result of the bicarbonate."

39 Fed. Reg. 29013

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Finally, the agency states its conclusion that "Alevaire is a fixed combination drug product." However, in recognition of the possibility that it is a single-entity drug, and in an attempt to afford plaintiffs every possibility of demonstrating effectiveness, the notice allows them to submit evidence to show Alevaire's effectiveness either as a fixed combination or as a single-entity drug.* In either case,

*"It is the present conclusion of the Bureau of Drugs, based in part upon the explicit labeling for Alevaire used until 1970, that Alevaire is a fixed combination drug product and that evidence of its effectiveness should be derived from adequate and well-controlled studies meeting the requirements of 21 CFR 314.111 and 21 CFR 3.86. Any request for a hearing with respect to the present notice should provide such evidence of effectiveness as a fixed combination or, alternatively, demonstrate that Alevaire is a single entity drug product and provide evidence in the form of adequate and well-controlled studies meeting the requirements of 21 CFR 314.111, that Alevaire is effective as a single entity drug product."

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the plaintiffs would be required to test the active ingredient or ingredients against the other elements of the drug, which they have studiously avoided doing to date. Indeed this has been the single demand consistently put forward by the agency since 1969, and the one with which plaintiffs have repeatedly refused to comply, because, one must speculate, such studies would reveal that the very effect claimed to result from their miracle-ingredient tyloxapol, can actually be achieved by the vehicle of sodium bicarbonate, glycerin, and water alone, as the agency feels.

Faced with the new notice which finds the drug to be a fixed combination drug but permits plaintiffs to properly demonstrate that it is only a single-entity drug, the plaintiffs have submitted no data whatsoever and resort here to two specious legal claims in an attempt to block the proceedings. First, it is claimed that the agency cannot proceed to withdraw the drug on the single-entity theory because such proceedings are barred by the doctrines of res judicata and collateral estoppel. Second, it is claimed that the agency cannot proceed on the fixed combination theory because it lacks the statutory prerequisite of "new information" of ineffectiveness

necessary to institute such proceedings. As will be shown, these claims derive respectively from a complete misunderstanding of the Court of Appeals decision and a misreading of the statutory language. A proper reading of both reveals that by its August 13 notice, the agency has fully complied with both the opinion and the statute.

THE PLAINTIFFS' CLAIM THAT THE INTERNATIONAL
FINANCIAL INSTITUTIONS OF THE UNITED STATES
BY THE INSTRUCTIONS OF THE UNITED STATES AND CONGRESSIONAL
INVESTIGATION BY CONGRESS AS A VIOLATION OF THE
AND CONGRESSIONAL INVESTIGATION AS A VIOLATION
CLAIM AND IS BASED UPON A REVERSAL OF THE
OPINION OF THE COURT OF APPEALS.

It is plaintiffs' position that by its own actions in withdrawing previous orders based on the single-entity theory, the agency has conceded, and that in its opinions, the Court of Appeals itself has affirmatively held, that "the effectiveness of [Alevaire] was established in the prior proceedings by the Miller-Faer and Cohen studies," and therefore that "the defendants may not be allowed to relitigate the validity of the evidence proving Alevaire's effectiveness as a single-entity drug." [Plaintiff's Memorandum at 11]

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This Court is therefore requested to "enjoin defendants from litigating the issue of whether Alevaire must be tested in comparison with its vehicle solution of waters, sodium bicarbonate, and glycerine" [Plaintiffs' Memorandum at 17]. This argument totally misreads the holding of the Court of Appeals.

Concisely stated, the Court of Appeals held that the agency had not given plaintiffs proper notice of the basis upon which it ultimately withdrew approval of the drug and had thereby deprived them of the opportunity to submit evidence in support of their request for a hearing. By no stretch of the imagination did the Court of Appeals hold (a) that plaintiffs had shown Alevaire to be "effective" within the meaning of the Act, or (b) that Alevaire need not be tested in comparison with its vehicle solution. It must be remembered that the issue before the Court was not whether Alevaire was effective or whether the submitted reports were properly controlled but only whether the agency had acted properly in refusing to hold a hearing before withdrawing approval of the drug.

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The Court of Appeals thus had no occasion to pass upon either the drug's effectiveness or the propriety of the agency's rejection of the studies purporting to test the drug as a single-entity drug. As noted, the August 7th order was predicated on a fixed combination theory. The March order, which was predicated on a single-entity theory was found by the court to have been withdrawn and the issues raised with respect thereto held moot. Accordingly, the court did not hold that, nor did the agency concede, that plaintiffs had demonstrated the effectiveness of Alevaire as a single-entity drug.

The issue before the Court of Appeals was a very different one, namely whether or not the agency had acted properly in withdrawing approval of Alevaire without a hearing. In determining whether the agency had acted in accordance with the applicable statutes and regulations, the Court of Appeals observed that the August 7th order, denying a hearing and withdrawing approval of Alevaire, was actually the agency's decision following the granting of plaintiffs petition for

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reconsideration of a similar order issued in March. Under 21 USC §355(e) and the applicable regulations, the August 7th order could follow only upon the issuance to plaintiff of notice and an opportunity to submit evidence in support of a request for a hearing. The Court traced the procedural history of the proceedings and observed that "That order was predicated on the Notice of Opportunity for Hearing of December 1, 1969 which was the only notice ever given to petitioners." The Court then looked at the specific grounds for withdrawal stated in the 1969 notice, and repeated in the various withdrawal orders issued and retracted in the interim, and compared it with the grounds upon which approval was ultimately withdrawn in the August 1973 order.

As the Court observed:

The August 7, 1973 order was the first time the fixed combination theory had been injected into the proceedings. There was no mention of that theory as a ground for proposed withdrawal in the Notice of Opportunity for Hearing of December 1, 1969. Petitioners were never given a meaningful opportunity to submit studies or data to contravene that theory. Instead, they were arbitrarily denied the opportunity to which they were entitled to establish their right to a hearing on that ground. (footnote omitted)

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This was the holding of the Court of Appeals. Accordingly, it did not pass upon the validity of the single-entity theory or the adequacy of the proof submitted, but held that there had been improper notice. Moreover, had there been proper notice, the most the Court could have done would have been to review the agency's decision and hold that there was sufficient evidence to require a hearing. In no case would the Court have passed upon either the effectiveness of the drug or the adequacy of the evidence submitted, prior to the holding of a hearing before the agency.

Thus, neither in the agency proceedings nor in the proceedings before the Court of Appeals was it held that in fact the plaintiffs had carried out "adequate and well-controlled" experiments such as would require a hearing before the agency, or that the effectiveness of Alevaire as a single-entity drug had been demonstrated by them. Accordingly, there is nothing to plaintiffs' present claims that res judicata bars the present agency proceedings. The principle of res judicata bars only the re-litigation of a question of fact or law actually determined between the same parties

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or their privies in a prior action. Southwest Pacific R. Co. v. United States, 168 U.S. 1 (1897); Williams v. Kalamazoo, 360 F. Supp. 554 (SDNY 1973); Holcott v. Hutchins, 245 F. Supp. 573 (SDNY), aff'd, 365 F.2d 833 (CA 2 1966). The doctrine of collateral estoppel serves to bar re-litigation of a fact, question or right in a subsequent suit but based on a different cause of cause provided that the issue was actually litigated and determined and was material and necessary to that prior decision. Comaf v. Sunnen, 333 U.S. 591 (1948); Cromwell v. County of Sac, 94 US 351 (1877); Irving National Bank v. Law, 10 F.2d 721, 724 (CA 2 1926). See generally 15 Moore's Federal Practice, § 0.405-7, 0.441-3. As the government has demonstrated, there was no such determination in the prior proceedings since the issues ultimately decided there were either procedural, as in the Court of Appeals, or in fact not finally determined, as in the agency proceedings. As between the parties to the present litigation, there was no finding that Alevaire had been demonstrated to be an effective single-entity drug or that it need not be tested against its own vehicle solution but only that there was improper notice. Had the agency again attempted to withdraw approval without proper notice, res judicata or

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collateral estoppel could perhaps have been invoked. Instead, the agency issued a new notice and has now afforded plaintiffs an opportunity to request a hearing and to present evidence in support of that request pursuant to the statutory scheme.

Plaintiffs have in fact requested a hearing but to date have submitted no additional evidence to support their claims. If the agency ultimately withdraws approval, plaintiffs can then invoke judicial review by the Court of Appeals to determine whether the agency acted properly in finding a lack of sufficient evidence to warrant denial of a hearing. There is, however, no merit to the claim that the agency is barred from proceeding on the single-entity theory by the doctrine of res judicata or collateral estoppel since the agency did not ultimately withdraw approval on that basis nor did the plaintiff prevail thereupon in their appeal.

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Even less substantial than the baseless invocation of the doctrines of ~~the judicial~~ and collateral estoppel is plaintiffs' claim that the agency is barred from proceeding against Alevaire as a fixed combination drug in the absence of "new information" as to its lack of effectiveness.

21 U.S.C. §355(c) requires that the Secretary withdraw approval of any application if he finds "on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved," that there is a lack of substantial evidence of effectiveness."

In the case of Alevaire, such "new information" is clearly provided by the results of the NAS-NRC study, and by the agency's re-evaluation of that and other data resulting in the conclusion that Alevaire is a fixed-combination drug.

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Plaintiffs again assert a res judicata type claim, arguing that because the agency relied on that study previously in attempting to withdraw approval of Alevaire, the HAS-IMS study is no longer "new information." Plaintiffs again fail to recognize that the initial proceedings were never in fact completed but, due to procedural defects, have been re-initiated on several occasions. It seems clear both as a matter of statutory construction and as a matter of agency practice that "new information" as used in §355(c) means any information made available after the application was initially approved. The statute itself instructs the secretary to act

"on the basis of new information before him ... evaluated together with the evidence available to him when the application was approved."

The obvious intent of the Congress was that all available information be considered, whether obtained prior to or after approval was granted. While the agency was obviously not to be permitted to grant approval and then without any additional information to simply change its mind and withdraw approval, when further or new information did come to light, the agency was

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not to be bound by its initial decision to grant approval. New information thus refers to any information made available after approval has been granted.

Further, nothing in the statute indicates that the agency is only permitted to use a report or other evidence once and must then disregard that information in future proceedings. The obvious-intent of Congress was that all information be considered, whenever gathered, in assessing effectiveness. Clearly, the agency cannot be required to disregard the MAS-MRC study simply because it has been the basis of prior but unconsummated agency proceedings. Although this precise issue has apparently not been passed upon before, it has been held in Bell v. Goddard, 366 F.2d 177 (CA 7 1966), that approval of a drug can be withdrawn on the basis of a new application of existing information, such as a re-evaluation of previous clinical studies. Although arising in the context of an allegedly "unsafe" rather than an "ineffective" drug, which placed an even greater burden on the agency, the court there held that:

We think that section 506(e) did not restrict the grounds for suspension to wholly new tests of a drug arising after the effective date of the application. The words "clinical experience" must be held to include such experience both prior and subsequent to the effectiveness of the petitioner's application...Since the petitioner's application had become effective, the burden

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of pending studies into "unsafe" at the time of the proceedings on the FDA. But this factor could not be compensated by conflicting relevant data existing when the application was approved. In this case an extensive reevaluation, which drew together clinical evidence in a matter not previously considered and which perhaps brought the full report to the attention of the agency for the first time, provided the basis for the Commissioner's findings. An interpretation of the statute prohibiting such a new application of existing information would do violence to the paramount interest in protecting the public from unsafe drugs. The fact that the re-evaluation may have been inspired by a change in administrative policy is irrelevant. (366 F. 2d at 177)

In response to a similar argument in Upjohn Co. v.

Finch, 422 F. 2d 944 (CA 6 1970), the court, citing

Bell v. Coddard, went on to read the "new information"

language to mean information made available since approval was granted, holding:

"We conclude from the record that FDA had additional information and evidence in 1969, when the certifications were revoked, which were not available to it in 1956 when Panalba, a fixed combination drug, was first certified as safe and effective."
422 F. 2d at 951

In the Alevaire case, aside from the agency's re-evaluation of the various studies, the proceedings initially commenced have never in fact been consummated with a

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determination of effectiveness or ineffectiveness.

Rather, procedural defects have caused the agency to recommence the initial action. Accordingly, the HAS-NRC study is clearly new information of precisely the type Congress envisioned the agency would use.

Further support for this view is found in the Court of Appeals decision, under which it was clearly envisioned that upon correcting the prior defective notice, the agency could thus proceed on the fixed combination theory. The Court, making no mention of the need to obtain "new information," instructed only that:

If the FDA proposes to withdraw approval of the NDA's for Alevaire on the ground that it is ineffective as a fixed combination drug, it must follow the procedure required by the statute and regulations. It must give the petitioners notice of the specific grounds proposed for withdrawal, an opportunity to present evidence showing that they are entitled to a hearing, and a hearing if that is shown to be required.

If anything, the plaintiffs are collaterally estopped from trying to avoid by this extraordinary action the procedurally correct final determination by the FDA as to the efficacy of Alevaire as a fixed combination drug.

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n-255IIIPLAINTIFF CANNOT OBTAIN JUDICIAL
REVIEW OF THE AGENCY'S ACTION IN
THIS COURT AT THIS TIME

Finally, plaintiffs cannot obtain judicial review of the agency's action at this time because they have failed to exhaust their administrative remedies. It is well settled that, with narrow exception, the federal courts will not interfere with an administrative proceeding or investigation and will first require the exhaustion of administrative remedies. M.G. Davis & Co. v. Cohen, 256 F. Supp. 128 (S.D.N.Y.) aff'd, 369 F.2d 360 (CA 2 1966); Thomson & McKinnon v. Securities and Exchange Commission, 268 F. Supp. 11 (S.D.N.Y. 1967). The rationale behind this doctrine is clearly stated by the Supreme Court in Aircraft & Diesel Corp. v. Hirsch, 331 U.S. 752, 767-68 (1947):

"The doctrine, wherever applicable, does not require merely the initiation of prescribed administrative procedures. It is one of exhausting them, that is, of pursuing them to their appropriate conclusion and, correlatively, of awaiting their final outcome before seeking judicial intervention. (emphasis added).

The very purpose of providing either an exclusive or initial and preliminary administrative determination is to secure the administrative judgment either, in the one case, in substitution for judicial decision or, in the other, as foundation for or perchance to make unnecessary later judicial proceedings. Where Congress had clearly commanded that administrative judgment be taken initially or exclusively, the courts have no lawful function to anticipate the

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administrative decision with their own . . . To do this not only would contravene the will of Congress as a matter of restricting or deferring judicial action. It would nullify the congressional objects in providing the administrative determination."

To date, plaintiffs have not submitted any evidence in support of their request for a hearing and more importantly the agency itself has not yet rendered an order withdrawing the drug. As the Seventh Circuit held in similar circumstances in Rutherford v. American Medical Association, 379 F. 2d 641, 643 (CA 7 1967):

"Only after action by the FDA is court review appropriate and provided for by statute. 21 USC §355(h)"

The court then went on to affirm the district court's action in discussing that suit for an injunction.

Even had the agency taken final action, there is substantial doubt that plaintiffs are proceeding in the proper forum. Under 21 U.S.C. §355(h), judicial review of agency action withdrawing approval of a drug may be had only in the Court of Appeals. Thus the proper procedure in order to secure the injunction plaintiffs seek can only be obtained by applying to the Court of Appeals for a stay pending review of any final withdrawal order, if it is forthcoming, as was done in American Cyanamid v. Richardson, 456, F. 2d

509 (CA 1 § 971).*

Thus, in view of both the failure to exhaust and the improper forum, the government would respectfully suggest not only that the motion for an injunction be denied but that the case itself be dismissed.

*If plaintiffs prevail at the administrative level, of course, the need for court review is obviated. If they lose at the administrative level, the Court of Appeals can review all their claims, together including the claims raised in this action. Stated in another way plaintiffs have an alternate remedy at law for this very relief.

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PLAINTIFFS HAVE FAILED TO
DEMONSTRATE THAT A PRELIMINARY
INJUNCTION SHOULD ISSUE

The power to grant a preliminary injunction lies within the trial court's discretion and is one which should be sparingly exercised. Docket v. Independence Shares Corp., 311 U.S. 282 (1940); Checkers Motors Corp. v. Chrysler Corp., 405 F.2d 319 (CA 2), cert. denied, 394 U.S. 999 (1969). Such an injunction, issued as it is prior to a trial on the merits, is an "extraordinary" and a "drastic" remedy, American Metropolitan Enterprises of New York, Inc. v. Warner Bros. Record, Inc., 389 F. 2d 903 (CA 2 1968), and should not be granted unless the movant carries the burden of persuasion by a clear showing. Berrigan v. Norton, 451 F.2d 790 (CA 2 1971); Robert W. Stark, Jr. Inc. v. New York Stock Exchange, Inc., 466 F. 2d 743 (CA 2 1972); Dopp v. Franklin National Bank, 461 F.2d 873 (CA 2 1972). The elements which made up that burden are generally: (a) the probability that the plaintiff will succeed on the merits, Hamilton Watch Co. v. Benrus Watch Co., 206 F.2d 738, 740 (CA 2 1953); (b) that the damage to the plaintiff in the absence of an injunction outweighs the foreseeable harm to the defendant, Penn Galvanizing Co. v. Lukens Steel Co., 468 F.2d 1021 (CA 3 1972); (c) that unless the injunction issues, plaintiff will suffer irreparable injury, for which he has no adequate remedy at law, Brown v. Chote, 411 U.S. 452 (1973),

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Prischman v. Dugand, 350 F. Supp. 79 (D.C.N.Y. 1972); and that the public interest will be served by the issuance of the injunction, United States v. UMW, 330 U.S. 258 (1947). See generally, Moore's Federal Practice ^{§ 265-1}. In the instant case it is clear that plaintiffs have failed to carry their burden with respect to these elements and that accordingly a preliminary injunction cannot and should not issue.

(a) While the formulations of the standard for demonstrating the likelihood of prevailing on the merits are legion, see II Wright & Miller, Federal Practice & Procedure § 2948, n.54, the most common standard requires a showing of a "reasonable probability" of success. Without laboring the point any further, the preceeding discussion of the merits of this case demonstrates not only that plaintiffs have not shown such a probability of success but rather that they do not have even a reasonable possibility of success. As the government has shown, plaintiffs claims are founded upon a fundamental misreading of the opinion of the Court of Appeals, an erroneous reading of the applicable statutory language, and exhibit a failure to exhaust administrative remedies. On the strength of that showing alone, relief should be denied.

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Plaintiffs in the memorandum claim that they will suffer irreparable pecuniary injury and damage to the reputation of the drug if an injunction does not issue. The government of course acknowledges that the ultimate withdrawal of approval will undoubtedly cause monetary damage to the plaintiffs. In response to this, several points bear mentioning. First, any harm to the reputation of the drug which is likely to result from such action has in fact probably occurred already, and cannot be avoided or substantially mitigated now. More importantly, however, there is precedent for holding in such approval withdrawal cases, that even though the denial of an injunction or a stay will cause irreparable harm, where there is little likelihood of prevailing on the merits^(S) a challenge to the Commission's Order, no such relief will be granted. Thus, in American Cyanamid v. Richardson, 456 F. 2d 509 (CA 1 1971), when plaintiff, using the proper procedure, sought a stay from the Court of Appeals pending review, Judge Coffin wrote:

I therefore conclude that Lederle's chances of prevailing on the merits are not so substantial as to justify my granting a stay pending review. While the loss to be suffered in the interim may indeed be substantial, I also note that all products competitive with Ach-rocidin whose manufacturers have accepted the final order will be removed from the market as of its effective date.

See also Unjohn v. Finch, supra at 950. Here too it has been demonstrated that plaintiffs chances of prevailing on the merits are slight.

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Third, it bears repeating that plaintiffs have an adequate and proper remedy available to them at law, namely, an application to the Court of Appeals for a stay pending review, as seen in both the American Cyanamid case and in the Unjohn case. Their expected response, that even to await the outcome of the administrative proceedings would result in irreparable injury, has previously been rejected by the Court of Appeals in Home Loan Bank Board v. Mallonne, 196 F.2d 336, 357 (CA 9 1965) cert. denied 345 U.S. 952 (1953) when it held:

"Great emphasis is laid on the injury to ... [plaintiff] ... that would result from pursuit of the tendered administrative remedy, but this concept runs counter to the well-settled rule that no one is entitled to judicial relief for a supposed or threatened injury until the prescribed administrative remedy has been exhausted, and this is true though it be asserted (as here) that the mere holding of the prescribed administrative hearing would result in irreparable damage. See Hyers v. Bethlehem Shipbuilding Corp., 303 U.S. 41, 50-51 ...; Macaulay v. Waterman S.S. Corp., 327 U.S. 540, 544, 545 ...; Goldsmith v. U.S. Board of Tax Appeals, 270 U.S. 117, 123 ...; Federal Power Commission v. Arkansas Power & Light Co., 330 U.S. 802 ..." (196 F.2d at 380-381).

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Finally, it is submitted that such injury as will result is not reason enough to issue a preliminary injunction not only because of the unlikelihood that plaintiffs can prevail on the merits, but also when the public interest itself is considered.

Plaintiffs bithely assert in their memorandum that because there is no issue as to the safety of Alevaire, the public interest not only would not be jeopardized by the granting of an injunction but would be served by helping to retain on the market their efficacious drug. Plaintiff thereby totally ignore the public interest in the removal from the public market place of ineffective drugs which prompted Congress to amend the Federal Food, Drug, and Cosmetic Act in 1962. See particularly S. Rep. No. 1744, 87th Cong. 1st Sess. (1962). Not only does the continued sale of such drugs result in a fraud upon the public, bilking them of untold thousands of dollars, but also may threaten the health of many citizens genuinely in need of medication who are duped into purchasing and relying upon a drug which the FDA has determined to be ineffective. As the Senate Report on the 1962 bill itself stated:

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[Leading physicians] stressed that the marketing of a safe but ineffective drug may well be positively injurious to the public health. When an ineffective drug is prescribed, it is usually in place of an older but effective drug. The problem is compounded by the fact that usually a considerable period elapses between the time when a highly-advertised new drug is put on the market and when knowledge becomes widely disseminated among the medical profession that its performance falls seriously short of its claims." Senate Report at 37.

As the Commissioner of Health of the New York Department of Health stated in the Congressional Record:

"In short, the physician is bombarded with seductive advertising which fails to tell the truth, the whole truth, and nothing but the truth.

"This often misleads him into prescribing a new drug without adequate warning or information about its possible side effects and, indeed, without any solid clinical evidence that the drug is effective or is even as safe as the advertisers claim. It is not sufficient to say that some law in some book book presently forbids some of these practices. Long before governmental authorities are in a position to prove the illerality of these practices and get the cumbersome legal machinery into motion and remove the drug from the market, grave harm has been done * * * . 108 Cong. Rec. 19925

(emphasis added)

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n-255

It is therefore abundantly clear that there are substantial public interests, both financial and medical, militating against the issuance of the requested injunction.

The burden on plaintiffs resulting from the denial of this motion, moreover, are of little consequence beyond the aforementioned pecuniary losses, particularly since they may, following the withdrawal order, simply apply to the Court of Appeals for a stay of the Commissioner's order pending review.

Also, it must be noted that the FDA is presently operating under an order issued by Judge Bryant in the District of Columbia. In that case, the Court, concerned with agency efforts to afford drug manufacturers additional time in withdrawal proceedings, ordered a strict timetable into effect to insure that these drugs were promptly withdrawn from the market. In balancing the competing interests at stake, the Court observed:

Because the FDA has responsibility in matters which directly and literally affect the nation's health and welfare, it is one of the most important of all Federal regulatory agencies. Its enforcement stance must be well balanced, but nevertheless effective. A timid approach can vitiate whatever protection the Congress has created for the consumer. On the other hand, an overly zealous approach can ruin a drug manufacturer by destroying public confidence in its products. Thus, it is understandable that the agency might have legitimate concern for drug manufacturers who must comply with new statutory requirements, and surely the question of time necessary to adduce new evidence of ef-

JS:bj
n-255

ficacy is an important consideration in creating an administrative scheme for implementation of the statute.

However, the FDA must remember that it does not stand alone in this regard. At the very outset the Congress also was sensitive to this problem, and allowed a two-year grace period before the 1962 amendments were to become effective. When, as is the case here, the Congress has shown an awareness of a problem and has acted accordingly, it seems inappropriate for an agency to adopt procedures which extend the grace period far beyond that envisioned by the statute, and which effectively stay implementation of the Congressional mandate that drugs in the marketplace be both safe and effective.

American Public Health Assn. v. Veneman, 349 F. Supp. 1311 (D.D.C. 1972). A similar concern for the public welfare is obviously present in these proceedings. When these factors are weighed together, it seems abundantly clear that plaintiffs have failed to demonstrate their entitlement to this extraordinary relief, particularly in view of the extreme unlikelihood that they will prevail on the merits, the substantial public interests against the issuance of this injunction, and the availability of an adequate and readily available remedy at law. Accordingly, it is clear that the motion for a preliminary injunction must be denied.

JS:bj
n-255CONCLUSION

These proceedings involving the FDA's attempts to withdraw approval of Alevaire have now lasted some five years. For all but a few brief periods, plaintiffs have managed to keep their product on the market despite the FDA's determination in 1969 that it was ineffective. The government readily concedes that these proceedings have taken longer than is usual in such cases at least in part due to administrative errors by the agency itself. Without in any way attempting to excuse those errors, it must be pointed out that the program undertaken in 1968 pursuant to the 1962 amendments to the Act is a complex and comprehensive one, during which some such errors must inevitably be made as procedures are refined and standards set.

Throughout these proceedings, however, the agency has consistently attempted to get plaintiffs to undertake one simple series of tests, namely to test the active ingredient or ingredients in Alevaire against the vehicle solution. The reason for this is obvious. If Alevaire is no more effective than that solution despite the active ingredients, the public should not have to pay extra for such a product and should not be duped into accepting a less effective product making false claims. Whatever the past defects in notice or in compliance with agency procedures, the agency has been insistent

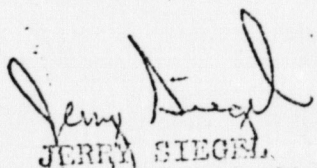
JS:bj
p. 255

on this one demand. Despite this, plaintiffs have studiously avoided undertaking any such study for some four years now. When finally confronted with proper notice and the agency findings, plaintiffs are now forced to resort to this diversionary action for it is clear that they have either not managed to conduct any such studies or, if they have conducted them, are not willing to publicize the results.

It is respectfully submitted that the plaintiffs motion for the extraordinary relief of a preliminary injunction must be denied.

Respectfully submitted,

PAUL J. CURRAN
United States Attorney for the
Southern District of New York
Attorney for Defendant



JERRY SIEGEL
Assistant United States Attorney

-Of Counsel.

PLAINTIFF'S REPLY BRIEF IN SUPPORT OF PRELIMINARY
INJUNCTION
A. 140

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----x
STERLING DRUG INC., WINTHROP
PRODUCTS, INC. and BREON
LABORATORIES, INC.,

Plaintiffs,

-v-

CASPAR W. WEINBERGER, Secretary
of Health, Education and Welfare,
and ALEXANDER M. SCHMIDT,
Commissioner of Food and Drugs,

Defendants.
-----x

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: 74 Civ. 4282 (LWP)
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PLAINTIFFS' REPLY BRIEF
IN SUPPORT OF MOTION
FOR PRELIMINARY INJUNCTION

Plaintiffs submit this brief in reply to the piece of fiction which has been submitted by defendants in opposition to the motion for a preliminary injunction. If the issues were not so serious we would be more inclined to treat lightly this latest attempt by defendants to justify, somehow, their inconsistent, inaccurate, illegal and wholly indefensible record in this matter.

But, after six years of arbitrary conduct by an agency determined to cover its mistakes at any cost to the public or plaintiffs, we have lost our sense of humor. We submit that it is time to call a halt to agency action which cannot be justified by law, science or the public interest.

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
A. 141

I. DEFENDANTS MISSTATE THE ISSUES PRESENTED
TO THE COURT OF APPEALS AND MISINTERPRET
THE DECISION OF THAT COURT.

Defendants' memorandum is remarkable in its failure to describe the evidence and issues before the Court of Appeals and in its misinterpretation of the decision of that Court.

1. The Court of Appeals Decision is Final on the Issue of
Whether Alevaire Must Be Tested Against its Vehicle.

As defendants concede, the NAS-NRC panel which reviewed Alevaire found "there was a lack of evidence that the active ingredient in Alevaire, tyloxapol, was any more effective than water in thinning secretions in the lung." (Def. Br. 8). It was in response to this report, as concurred in by the FDA, that plaintiffs commissioned two new clinical trials to test the precise issue raised by the panel and Agency.

In June, 1970, the studies by Drs. Miller and Paez and Cohen were completed and submitted to the FDA. With FDA's advance knowledge, the studies compared Alevaire to water and saline. These controls were employed because they had been suggested by FDA and because they were logical and proper in that water and saline are commonly used alternatives to Alevaire as mucoevacuant agents. The studies were adequate and well-controlled as defined by FDA's own regulations and they proved Alevaire to be effective as a mucoevacuant and more effective than water and saline.

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
A. 142

Plaintiffs did not rest on their own opinion that the Miller-Paez and Cohen studies were adequate and well-controlled. Instead, they submitted those studies to a number of independent experts, "knowledgeable and experienced in the field", (Slip. Op. 3126), from some of the leading institutions in America. Each of these experts then made affidavits attesting that the studies were adequate and well-controlled and proved Alevaire to be effective and more effective than water and saline.

In September, 1971, the FDA issued a withdrawal order rejecting the Miller-Paez and Cohen studies as allegedly being not adequate and well-controlled. After plaintiffs appealed and filed their brief in the Court of Appeals documenting the fallacious nature of FDA's criticisms, the Agency moved successfully to remand the matter for further consideration.

Over a year later, in March, 1973, FDA issued another withdrawal order which raised a new argument that the Miller-Paez and Cohen studies were not well-controlled because the only proper test would be to compare Alevaire against its "inactive" vehicle, i.e., an aqueous solution of sodium bicarbonate and glycerin. 38 Fed. Reg. 6308 (Complaint Ex. 2).^{*} Plaintiffs

^{*}Defendants make the remarkable statement that "consistently ... since 1969" the Agency has demanded that Alevaire be tested against its vehicle. (Def. Br. 18). Yet, the Court of Appeals found that this theory surfaced "for the first time", (Slip. Op. 3127), in the March order and, of course, it was abandoned in the August 1973 order.

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
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promptly submitted a Petition for Reconsideration thoroughly rebutting this newly raised contention, as well as all others made in the March order.

This, then, was the central issue before the Court of Appeals with regard to the March, 1973 withdrawal order. Contrary to the assertions in defendants' memorandum herein, the procedural issue of lack of notice was never raised concerning the March, 1973 order.

We submit that an analysis of the Court of Appeals decision makes it clear beyond the shadow of a doubt that the Court considered this issue, found that the FDA had conceded its position to be erroneous in this regard, and that the Agency had abandoned its argument and terminated its proceedings insofar as they were based on the proposition that Alevaire had to be tested against its own vehicle.

In short, it is simply an exercise in creative writing for defendants to argue that the proceedings culminating in the March order were dismissed on procedural grounds. (Def. Br. 24). The Court of Appeals certainly determined, on the express concession of the government, that Alevaire need not be tested against its vehicle and that the issues raised in the March order were conclusively abandoned by defendants.

2. Defendants Cannot Avoid the Res Judicata or Collateral Estoppel Effect of the Court of Appeals Decision.

Defendants argue, on more technical grounds, that the

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
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Court of Appeals decision as to the March order is not final or on the merits since the appeal from that order was dismissed as moot. The argument is specious since the defendants themselves, by revoking the March order and abandoning it as substantively erroneous, caused the matter to become moot. We note that the Court denied defendants' initial motion to dismiss the appeal as moot and thus preserved its jurisdiction to comment fully on the merits. In its decision, the Court made such comment and it made clear that the only mootness was in terms of the relief requested. The Court reasoned that since FDA had already revoked the March order and reinstated approval of the NDA's, it would be meaningless for the Court to grant the same relief. (Slip. Op. 3128-3129).

Where, as here, defendants by their own action in abandoning the grounds asserted in the March order caused the dismissal for mootness, the law is clear that they cannot prevent the application of res judicata or collateral estoppel.

Professor Moore discusses the issue in the context of appellate review of lower court judgments, but the principles are clearly applicable here as well:

"If the appellant is responsible for the intervening change in the status quo that makes appellate review impossible, it is difficult to see why he should be regarded any differently from a party who, having lost in the trial court, has failed to take his appeal within the time allowed by statute. It would be quite destructive to the principle of judicial finality to put such a litigant in a position to destroy the collateral conclusiveness of a judgment

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION

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by destroying his own right of appeal ... And the same is true when the appellant, by conceding an issue in the appellate court, renders the case moot. Otherwise, any litigant unsuccessful in the trial court could deprive the judgment of collateral estoppel effect by appealing on two grounds, both necessary if the judgment is to be reversed, and then conceding one of them in the appellate court." 1B Moore's Federal Practice, ¶0.416[6], pp. 2327-28 (1974)

These principles were applied in this Circuit in Cover v. Schwartz, 133 F. 2d 541 (2nd Cir. 1943) cert. denied 319 U.S. 748 (1943). There, Judge Frank stated:

"This case has not become moot because of intervening circumstances over which appellant had no control. ... For appellant, who asserted and tried to show infringement in the court below, so that there was a controversy before that court, in this court concedes that there is no infringement by defendant, which means that there is now no controversy. Although appellee did not ask for a declaratory judgment on the basis of threatened suits by appellant ... nevertheless dismissal of the suit, as distinguished from dismissal of the appeal, might result in unfairness to appellee by subjecting him to other vexatious actions by appellant. ... We shall, therefore, merely dismiss the appeal, with the consequence that the judgment of invalidity made by the trial court will stand as entered."
133 F. 2d at 546-547.

Here, plaintiffs are in the same posture as the appellee in Cover v. Schwartz. Plaintiffs were perfectly willing to litigate the issue of the adequacy of the Miller-Paez and Cohen studies, but, when plaintiffs appealed to the Court of Appeals from FDA's order on those studies, FDA thereupon conceded that its analysis of those studies had been erroneous, abandoned the grounds

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
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asserted in the March order as a basis for proceeding against Alevaire, and stated in the Court of Appeals that the adequacy and well-controlled nature of the Miller-Paez and Cohen studies was no longer an issue being contested by the government.

Accordingly, the entire prior proceeding was terminated by and became merged in the decision of the Court of Appeals and was not, as the defendants now contend, merely an "unconsummated" proceeding. Defendants' new attempt to litigate previously decided issues represents the continued "unfairness to [plaintiffs here] by subjecting [them] to other vexatious action by [the government]" deplored by the Court in Cover v. Schwartz, supra at 547, and should not be countenanced by this Court. See also Electrical Fittings Corp. v. Thomas & Betts Co., 307 U.S. 241 (1939). U.S. v. Munsingwear, Inc., 340 U.S. 36 (1950); So. Pac. Term. Co. v. ICC, 219 U.S. 498 (1911).

3. Defendants in Effect Concede They Lack the Requisite "New Information" to Support their Fixed Combination Proposal.

In their brief, defendants' only showing of "new information" is their statement:

"In the case of Alevaire, such 'new information' is clearly provided by the results of the NAS-NRC study, and by the agency's re-evaluation of that and other data resulting in the conclusion that Alevaire is a fixed-combination drug."
(Def. Br. 26)

But that NAS-NRC report is obviously insufficient as a basis for the fixed combination proposal.

Defendants' mistake is in failing to separate the two distinct parts of their new proposal. We have never contested that the NAS-NRC report served as the "new information" required for the proceedings which began in 1968. But those proceedings terminated last May with the decision of the Court of Appeals and the report of the NAS-NRC panel was merged into that termination.

Thus, the NAS-NRC report cannot serve as the "new information" required for the fixed combination proposal. That is clear from the face of the report which makes no reference to Alevaire as a fixed combination. To the contrary, as defendants concede, that report considered Alevaire to have a single active ingredient, tyloxapol (Def. Br. 8). Moreover, since the NAS-NRC review panels themselves created the classification "ineffective as a fixed combination" (Slip. Op. 3130) prior to the date defendants set forth in their brief for the agency's formal promulgation of the combination drug regulations, it is apparent that had the panel considered Alevaire to be such a drug, it would have labeled it as such.

Defendants' reliance on Bell v. Goddard, 366 F. 2d 177 (7th Cir. 1966) and Upjohn Co. v. Finch, 422 F. 2d 944 (6th Cir. 1970) is misplaced. In Bell, the Court considered "an extensive re-evaluation, which drew together clinical experience in a manner not previously attempted ..." (366 F. 2d at 177) as meeting

the statutory requirement. Here, there is no showing of any "intensive re-evaluation ... of clinical experience." Rather, there is only the Agency's last minute about-face, on the heels of the Supreme Court's decision in Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 1973), from a theory which had been shown to be without substance, to a fixed combination theory which the Court of Appeals found unpersuasive. (Slip. Op. 3137).

In Upjohn, the company claimed that the FDA had no new information or evidence before it with respect to the drugs in question. The Sixth Circuit rejected this contention, stating:

"The record demonstrates to the contrary. At the time he revoked the certifications the Commissioner had before him the unanimous conclusion of thirty experts in antimicrobial therapy that the products in question are ineffective as fixed combinations." 422 F. 2d at 944.

In sharp contrast, the Commissioner here has no experts or new data to support his proposal that Alevaire is a fixed combination. Upjohn hardly supports defendants; rather, it demonstrates the lack of basis for FDA's proposal herein.

4. The Doctrine of Exhaustion of Administrative Remedies Does Not Apply Where Agency Action is Contrary to Law, Inconsistent With A Controlling Statute, or In Violation of Due Process.
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Despite the defendants' assertions, the plaintiffs are not required to exhaust their administrative remedies in the case at bar.

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At the outset, we note that a principal ground of our attack on defendants' proposal is that it is barred by res judicata and collateral estoppel. Obviously, it would be a total perversion of those equitable doctrines if plaintiffs were forced to relitigate previously decided matters and then argue res judicata on appeal only.*

Both by attempting to relitigate previously decided matters and in proceeding without the requisite statutory base, defendants are proceeding in violation of law. In so doing, they are subject to injunction by this Court, Leedom v. Kyne, 358 U.S. 184 (1958). In fact, as far as it involves a construction and application of the term "new information", the case closely resembles Jewell Companies, Inc. v. Federal Trade Commission, 432 F. 2d 1155 (7th Cir. 1970). In Jewel, it was held that a district court could temporarily enjoin an FTC proceeding while the court decided a question of statutory construction concerning the scope of the Commission's discretion.

Here, the question of whether defendants possess the requisite "new information" is particularly appropriate for review at this time. In the first instance, the lengthy history of this proceeding and the decision of the Court of Appeals raise serious

*It is apparent, of course, that defendants, by the very act of bringing the new proposal, and by their answering papers, have determined that they are not barred from proceeding. Thus, no relief can be expected within the Agency.

questions concerning the way in which the FDA developed its fixed combination theory. Moreover, if plaintiffs are forced to proceed through a hearing, the Commissioner can then create his "new information" after the fact. On appeal, the question would be whether the decision was supported by substantial evidence with the usual great weight given to "administrative expertise." The issue of whether there was sufficient "new information" to warrant institution of the proceedings in the first instance would be lost.

Since Congress intended that no withdrawal proceeding be instituted without such "new information", and under the peculiar circumstances at bar, the question is ripe for review, and in the absence of such information the proceeding should be enjoined.

A case in point is Elmo Division of Drive-X Co. v. Dixon, 348 F. 2d 342 (D.C. Cir. 1965), where the court reasoned that an agency proceeding brought in violation of its own rules could be enjoined since it would be futile for plaintiff to have to exhaust his remedies before raising the impropriety of the proceedings. This reasoning applies not only to the "new information" argument, but, of course, to the res judicata argument as well.

In sum, plaintiffs are not required to submit to illegal agency action before seeking relief.*

*It is apparent that this type of relief is appropriately sought in this court. Defendants' reliance on 21 U.S.C. §355(h) is misplaced since that section is applicable only on appeal from final withdrawal orders.

Alternatively, plaintiffs are entitled to proceed in this Court at this time to enjoin a deprivation of their Fifth Amendment right to Due Process. Defendants' illegal proceeding to withdraw existing approvals of plaintiffs' new drug applications constitutes a deprivation of a property right in violation of due process. Fay v. Douds, 172 F. 2d 720 (2nd Cir. 1949). And plaintiffs are entitled to relief from being forced to the time, expense and notoriety of litigating in a clearly illegal administrative proceeding. See Public Utilities Comm. v. United Fuel Gas Co., 317 U.S. 456 (1946).

We submit that the doctrine of exhaustion of administrative remedies is inapplicable here and that the Court can and should properly exercise its jurisdiction to enjoin improper administrative acts which have and are causing grave and irreparable injury to plaintiffs.

5. Judge Bryant's Order in American Public Health Association v. Veneman Is Not Applicable to this Proceeding.

It is not clear why defendants cite and attach to their papers the order of Judge Bryant of the District of Columbia in American Public Health Ass'n v. Veneman, 349 F. Supp. 1311 (D.D.C. 1972).

In a telephone conversation on October 9, defendants' counsel relied on this decision as barring plaintiffs' request

for an adjournment of the October 15 filing deadline until, if necessary, 30 days after this Court rules on the preliminary injunction motion. It would appear that this reliance is misplaced since, as the reported decision makes clear, Judge Bryant's order was in the general context of FDA's failure to release and implement NAS-NRC reports. Clearly, the decision and order are not applicable to Alevaire since, four years earlier in July 1968, FDA had released the NAS-NRC report concerning Alevaire and, by August 1972, had already issued the first of its withdrawal orders.

In the current circumstances, where there have been three withdrawal orders and a fourth new proposed withdrawal, we would think defendants would agree that they are not bound by Judge Bryant's order in this specific case.

In any event, the order by its terms applies only to administrative adjournments by the Agency and clearly is not binding on the power of this Court to grant whatever equitable relief it deems appropriate under the facts at bar.

6. The Grant of a Preliminary Injunction Is in the Public Interest.

Defendants concede that Alevaire is a perfectly safe product but argue, in typical fashion, that:

"Not only does the continued sale of such drugs result in a fraud upon the public, bilking them of untold thousands of dollars, but also may threaten the health of many citizens genuinely in need of medication who are duped into purchasing and relying upon a drug which the FDA has determined to be ineffective." (Def. Br. 38).

In response to this bombast we note that Alevaire is sold by prescription only and primarily to hospitals. In addition, its basic effectiveness has never been questioned; the only question has been whether it is more effective than the bland mucoevacuants such as water and saline. The Miller-Paez and Cohen studies in fact proved it to be more effective than saline and water. Thus it is the government here which is attempting to remove from the market and deprive patients of the most effective mucoevacuant agent available.

Moreover, despite defendants' current rhetoric, twice before when plaintiffs appealed to the Court of Appeals, the Agency voluntarily granted administrative stays pending appeal. Those administrative stays, of course, came in the context of appeals from final orders of withdrawal where the Agency had presumably reviewed the evidence and made a considered judgment. Here, there is only a proposal to withdrawal, yet somehow defendants' view of the public interest has changed. This is hardly surprising in view of defendants' record of inconsistency throughout these proceedings.

PL'S. REPLY BRIEF FOR PRELIMINARY INJUNCTION
A. 154

We submit that, as the Court of Appeals noted, the public interest here lies in keeping an effective drug on the market. (Slip. Op. 3134-3135, n. 13). The injunction should be granted.

Respectfully submitted,

ROGERS HOGE & HILLS

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James H. Luther
Roger M. Rodwin
Sterling Drug Inc.

STIPULATION AND ORDER
A. 155

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----X
STERLING DRUG INC., WINTHROP PROD- :
UCTS, INC. and BREON LABORATORIES, :
INC., :

Plaintiffs, : 74 Civ. 4282 (LWP)

v. :

CASPAR W. WEINBERGER, Secretary of :
Health, Education and Welfare, and :
ALEXANDER M. SCHMIDT, Commissioner :
of Food and Drugs, :

Defendants. :
:-----X

STIPULATION

IT IS HEREBY STIPULATED AND AGREED, by and between the parties hereto by their respective counsel, that the time in which plaintiffs may file the data, information and analyses on which they rely to justify a hearing regarding defendants' notice entitled "Alavaire: Opportunity for Hearing on Proposal to Withdraw Approval of New Drug Applications," 39 Fed. Reg. 29013-29014 (August 13, 1974), be and hereby is extended from October 15, 1974 to 15 days after the filing of the decision of this Court on plaintiffs' motion for a preliminary injunction herein, in the event said motion be denied in whole or in part.

ROGERS HOGE & HILLS

By Jane B. Lurie
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90 Park Avenue
New York, N.Y. 10016
(212) 953-9200

PAUL J. CURRAN
United States Attorney for the
Southern District of New York

So ORDERED: 10-23-74

J. W. Pierce

By [Signature]
Assistant United States Attorney
Attorneys for Defendants

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

STERLING DRUG, INC., WINTHROP PRODUCTS, INC. and BREON LABORATORIES, INC.,

Petitioners

-vs-

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, ALEXANDER M. SCHMIDT, Commissioner of Food & Drug Administration,

Respondents.

74 Civ 4282

October 10, 1974
9:30 A.M.

B E F O R E :

HON. LAWRENCE W. PIERCE,

District Judge.

A P P E A R A N C E S :

ROGERS, HOGE & HILLS, ESQS.,
Attorneys for Petitioners
WILLIAM F. WEIGEL, ESQ.,
JAMES B. SWIRE, ESQ.,
E. CARRINGTON BOGGAN, ESQ., and
ROGER RODWIN, ESQ., of Counsel

JERRY SIEGEL, ESQ., and
JEFF SPRINGER, ESQ.,
Attorneys for Respondents

ALSO PRESENT:
JOHN SIFFERT, ESQ.

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THE CLERK: Sterling Durg, Inc. et al versus
Caspar W. Weinberger, Secretary of Health, Education and
Welfare et ano.

Is the plaintiff ready?

MR. WEIGEL: Yes, your Honor.

THE CLERK: Defendant ready?

MR. SIEGEL: Yes.

THE COURT: Appearing for the plaintiff
from the firm of Rogers, Hoge & Hills is Mr. Weigel, Mr.
and Mr. Redman, of Counsel,
Swire, Mr. Boggan, and appearing for the defendant Mr.
Siegel and Mr. Springer.

MR. SIEGEL: Yes, sir.

THE COURT: And seated with you is who?

MR. SIFFERT: Mr. Siffert.

THE COURT: I understand that both sides here
agree that there is no need for an evidentiary hearing
and that this can be disposed of by oral argument.

Is that correct, Mr. Weigel?

MR. WEIGEL: Yes, your Honor.

THE COURT: Mr. Siegel?

MR. SIEGEL: Yes, it is.

THE COURT: Perhaps, then, we can proceed more
expeditiously if the application here is consolidated
with trial on the merits pursuant to Rule 65.

1 gtjw

2 Is that satisfactory?

3 MR. SIEGEL: Yes, it is.

4 THE COURT: Counsel?

5 MR. WEIGEL: Yes, your Honor, provided all of
6 our documents are on the record.

7 THE COURT: I suppose that will necessarily
8 have to occur in order to make a record.

9 Any objection to documents submitted thus far
10 in connection with this matter constituting the record plus
11 the oral argument?

12 MR. SWIRE: Your Honor, if your Honor wishes,
13 we have here the appendix and our briefs to the Court of
14 Appeals. It is not clear yet whether that is necessary
15 or not.

16 THE COURT: No, I won't intend to incorporate
17 them as part of this record, although reference, no doubt,
18 will be made to what occurred there.

19 Moving papers, replies and memoranda submitted
20 by either side shall constitute the record.

21 Satisfactory?

22 MR. SIEGEL: Yes.

23 MR. WEIGEL: Yes.

24 THE COURT: Anything further?

25 All right.

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Let me see if I can briefly summarize the history behind this case and then against this backdrop counsel can make their oral presentations.

I would like to indicate at the outset that this history has been adopted from the recent Second Circuit opinion dealing with this matter.

It appears that a new drug application, a NDA, was approved for Alevaire, the drug here in question, in 1952 by the FDA. At that time, under the controlling statute, that is, the Federal Food, Drug and Cosmetic Act of 1938, only the safety factor was considered.

In 1962 the Act was amended to allow the FDA to remove drugs from the market if substantial evidence was lacking that the drug was effective for its intended use. To comply with this legislative mandate, the FDA retained the National Academy of Sciences, National Research Council, NAS-NRC, to review the effectiveness of each drug that had been approved up until then. Such a study was undertaken of Alevaire and the NAS-NRC concluded that the drug was ineffective for its intended use. The FDA concurred with this finding.

On December 1, 1969, the FDA published a notice in the Federal Register announcing its intention to withdraw its approval of the drug. Apparently it

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based its conclusion that the drug was ineffective primarily on the criticism of the NAS-NRC that Alevaire was no more effective than water.

To refute this finding and to support its request for a hearing, the plaintiffs submitted two studies, the Miller-Paez study and the Cohen study. The former compared the drug with water and saline and the latter compared it with water alone. Both studies concluded that Alevaire was an effective muceovacuuant.

On August 27, 1971, the FDA denied a request for a hearing on FDA's findings that these studies were not adequate and well controlled as defined in 21 CFR 130.12 Section A 52. Simultaneously, the FDA withdrew its approval of the drug. Thereafter, the plaintiffs appealed pursuant to 21 United States Code 355(h).

While the appeal was pending in the Second Circuit, the FDA terminated its order and moved to remand the case to the FDA for further administrative proceedings. The remand was granted on January 11, 1972.

On March 2, 1973 the FDA issued another order which, again, denied the request for a hearing and withdrew approval of the drug. However, this time the FDA indicated that water was not the proper control with which to compare the effectiveness of Alevaire. In its opinion,

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the proper control was stated to be Alevaire minus tyloxapol. Prior to this time the FDA had indicated that either water or Alevaire minus tyloxapol would be a proper control.

Plaintiffs requested a reconsideration of this order and also filed an appeal of the order.

On June 14, 1973, the FDA again terminated its then latest order and reinstated approval of the drug and the FDA also moved to dismiss the appeal from the March 2, 1973 order.

However, while a decision on its motion before the Court of Appeals was pending and even before oral argument was held on its motion, the FDA, on August 7, 1973, again issued another order denying the petitioner a hearing and again withdrawing approval of the drug. However, this time the FDA claimed that Alevaire was a "fixed-combination" drug within the meaning of 21 CFR 3.86. Accordingly, the FDA maintained that in order to support the effectiveness of the drug, studies had to be made ^{establishing} ~~as-receiving~~ the "contribution each of the three components of Alevaire makes to the claimed effectiveness of the drug."

Plaintiffs appealed this order.

The appeals from the March 2nd and August 7th

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orders were consolidated and on May 2, 1974 the Second Circuit rendered its decision. It dismissed the appeal from the March 2nd order as moot and it set aside the August 7th order and reinstated approval of Alevaire.

On August 13, 1974, the FDA published in the Federal Register its intention to withdraw approval of the drug on two alternative grounds. First, treating Alevaire as a single entity drug, the FDA maintained that it must be compared with its own vehicle, that is, a solution of two percent sodium bicarbonate, five percent glycerin and ninety-three percent water.

Second, treating Alevaire as a fixed-combination drug, studies had to be made assessing the contribution to the overall effectiveness of the water, the bicarbonate and the tyloxapol. and ^Cglycerin would be added to all the respective control groups.

Plaintiffs were given until September 12, 1974 to file a notice of appearance and request for a hearing, and until October 15, 1974 to furnish the FDA with the necessary information supporting the request for a hearing.

On August 15, 1974, the plaintiffs sought to have their time extended, but this request was denied.

On September 10, 1974, the plaintiffs requested a hearing on the matter. However, the data to support

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2 this request, it is my understanding, has not yet been
3 provided to the FDA.

4 This summary, I think, brings us to the
5 present action. I wonder if there are any corrections or
6 modifications of this statement as I have made it:

7 MR. WEIGEL: Your Honor, in requesting the
8 hearing in September under the August 13, 1974 order,
9 I would like to point out that we did so without prejudice
10 to our bringing this action.

11 THE COURT: All right.

12 MR. WEIGEL: We did not acknowledge the
13 propriety of the withdrawal order.

14 THE COURT: All right. Anything further?

15 All right. If not, I will hear argument from
16 the parties. First the movant.

17 MR. WEIGEL: If it please the Court, your Honor,
18 when the Court of Appeals consolidated the two orders,
19 the so-called March order and the August order, I think
20 it is important to see exactly what the Court had before
21 it.

22 It had the March order, which was based on the
23 adequacy of the tests that the plaintiffs had performed,
24 that is to say, whether or not water and saline were
25 proper controls inasmuch as they had been mentioned by

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2 the NAS, the FDA had concurred with them. That issue
3 was very definitely before the Court.

4 The Court refused in the first instance to --
5 well, refused to permit the FDA to withdraw the order
6 and dismiss the appeal until after it had actually
7 ruled upon it.

8 Now, granted in its opinion it did state that
9 that order had become moot, but it became moot only
10 because of the affirmative action of the government
11 and I do not believe that the government, and it is quite
12 clear, may not avoid the effect of res judicata by its
13 own affirmative action which causes this to become moot.
14 The Court said it was moot because we had the relief
15 which we had sought.

16 In our briefs we point out that Professor
17 Moore has a good discussion on that very point where
18 one himself has caused something to be moot that it
19 cannot avoid res judicata.

20 It is quite clear here since this very issue
21 comes up as part of the most recent August 14 order was
22 involved, it was for all purposes litigated, the plain-
23 tiffs herein were ready to go forward on that matter and
24 the government withdraw it and, in effect, frustrated us
25 from getting an adjudication on the merits and I think

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2 they are clearly bound by that as far as that is concerned.

3 The August order, which was based upon the
4 combination theory, the Court dismissed that because of
5 failure to give the plaintiffs herein proper notice of
6 the theory. As they pointed out, this was, you might
7 say, a last minute change that had been occasioned by
8 the Supreme Court's decision in the ^{Hynson} Hinson case, wherein
9 it became very clear that the Food and Drug Administration
10 could not succeed on its first theory and they had to come
11 up with a new theory, and they did come up with an
12 entirely new theory which had never been mentioned at
13 any time in the proceedings and the Court felt, in
14 effect, that this arbitrary switch was not proper since
15 we had no notice.

16 Now, the Court did say that there appeared to
17 be little in the record to support this new combination
18 theory, and I think we must bear in mind that part of
19 that record on which the Court of Appeals commented
20 included the NAS-NRC report. That is the only new
21 evidence or new information which was available to the
22 government to support either its March order or its
23 August order, and in the present order the government
24 concedes in its brief that the new information which is
25 a most important and critical statutory prerequisite to a

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2 withdrawal proceeding is that there be new information.

3 Now, the only new information that has been
4 available to the government has been that NAS-NRC report.
5 That NAS-NRC report did not mention the combination
6 theory. It made it quite clear that Alevaire was a single
7 ingredient drug in a vehicle. So, in effect, that new
8 information has been the subject of litigation which
9 was resolved in favor of the plaintiffs and ~~neither can~~
10 ^{can} it no longer, having ~~it~~ been the subject of such liti-
11 gation, support a new proceeding.

12 The Court did point out to the government if
13 they did want to proceed, yes, they could proceed, but
14 they must do so within the requirements of the statutes
15 and of its own regulations.

16 So we contend having litigated the question of
17 the controls and had it resolved satisfactorily in our
18 favor that the government may not, ^{Proceed} ~~proceed~~ and litigate
19 that theory, and as far as the new theory that we may be
20 a combination, there is no new information to support
21 that. We have already been through and litigated the
22 NAS-NRC report and it has been resolved favorably for
23 the plaintiffs herein.

24 The government came in on the first issue,
25 the so-called proper controls, and admitted, they conceded

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2 their error. They said they confessed judgment, as they
3 put it to the Court, and that appears, of course, in the
4 Court of Appeals opinion. They admitted it was erroneous.

5 I certainly think there is no basis on which
6 they can proceed on the same ground which they have had
7 before the Courts. They had six or more long years.
8 We have been to the Court of Appeals on four occasions,
9 we have had four notices of withdrawal. The damage
10 that has been suffered by the plaintiff is irreparable.
11 They cooperated with the Food and Drug, they made these
12 tests, they did these tests within the protocols that had
13 been suggested by the Food and Drug, they did everything
14 possible to maintain on the market a safe and effective
15 drug, a drug which at least ten experts, the top experts
16 in this country in this type of therapy, have all said
17 and submitted affidavits before the Courts and before the
18 agency that this is an effective drug and that the
19 controls for testing it which were used by the plaintiffs
20 ^{were} with the proper controls.

21 THE COURT: Of course, that may or may not be
22 the case, but it certainly is not for a United States
23 District Judge to determine, is it?

24 If a finding of that type is to be made, it
25 seems to me it has to be made somewhere other than here,

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2 either at the FDA laboratory level or the Court of Appeals
3 level.

4 MR. WEIGEL: We ask you here to make a find-
5 ing, in effect, that the matter has already been litigated
6 and we should not be forced to go through another long
7 administrative proceeding.

8 I point out that the last one took well in
9 excess of six years and three changes in theories. We do
10 believe you certainly may enjoin the government from pro-
11 ceeding and subjecting us to this highly illegal and
12 improper proceeding.

13 THE COURT: Here is the Court of Appeals
14 speaking on page 3137 in their opinion and after indi-
15 cating what the agency must do in order to provide the
16 opportunity for the petitioners here to be given a proper
17 opportunity to be heard and present what evidence they
18 have, the Court says:

19 "The FDA may then determine the question
20 on a full and proper record, subject, of course,
21 to petitioners' right of appeal to this court
22 from an adverse determination."

23 It seems to me the Court was saying that the
24 FDA was entitled to proceed, but they had to proceed
25 properly when it refers to a full and proper record.

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2 Are you suggesting that the Court of Appeals
3 had made some final determination about the efficacy of
4 this drug or, for that matter, had that issue really
5 before it?

6 MR. WEIGEL: I think the Court of Appeals
7 was saying, your Honor, that if the government proceeded
8 properly and lawfully within the statute and its regula-
9 tions and we were subjected to this procedure, that we
10 should have an opportunity to make a full and complete
11 record.

12 We say we have already made a full and complete
13 record, that it has been litigated, it has been resolved
14 in our favor and that the government, in raising -- that
15 is as far as the first issue, the March order, which was
16 held to be moot has been litigated.

17 As far as the new theory, the combination
18 theory, we contend that the government has not complied
19 with the very important statutory prerequisite that it
20 have new information.

21 THE COURT: Let us take the first.

22 Can you show me where in the opinion there
23 is reference to the March order that indicates that the
24 Court considered the merits of the control factors set
25 out in the March order?

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2 MR. SWIRE: Do you want each citation, your
3 Honor?

4 THE COURT: Perhaps if you can point me toward
5 the portion of the opinion which pertains to this, it
6 would be helpful.

7 MR. SWIRE: On page 3127, your Honor, in
8 discussing the March order, the Court refers to the fact
9 that our extensive rebuttal ⁱⁿ and the petition for re-
10 consideration was "apparently well taken." The two foot-
11 notes on that page, Footnote 6 and 7 -- Footnote 6
12 talks directly to the control and notes that in the
13 first withdrawal order the FDA itself had indicated that
14 "either water or Alevaire minus tyloxapol would be a proper
15 control," and they note in Footnote 7 in discussing the
16 petition for reconsideration, it included material "support-
17 ing the suitability of controls used in petitioners'...
18 studies," and I think we had -- well, the Court decision
19 then goes on and makes it very clear that it considered
20 the issuance of the August order plus the argument before
21 it to be an abandonment of all the grounds previously
22 raised.

23 So I think the quote your Honor referred to
24 at 3137 refers solely to the fixed-combination theory,
25 it gives them no leave to proceed again on the control

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2 theory.

3 I think on 3128, the Court specifically says,
4 "This third order," that is the August order, "abandoned
5 the grounds on which the prior two orders of March 2nd
6 and August 7th had been based," abandoned it.

7 Then on page 3129 they quote from the respondents'
8 brief which reflects the confession of error that was
9 made orally as well before the Court of Appeals and
10 they are quoting the respondents' the defendants' herein,
11 "We confess^{ed} error in that order of March 2nd before this
12 Court."

13 what they were confessing error to was the
14 substance.

15 MR. WEIGEL: The Court pointed out in the
16 next paragraph they conceded it was erroneous, but never-
17 theless we had our relief and, consequently, they declared
18 it to be moot on page 3129.

19 MR. SWIRE: And, your Honor, the only reason
20 we raise the point about the record is to indicate if
21 your Honor wishes that these issues were specifically
22 before the Court of Appeals. These affidavits were in
23 the record and the refutation was complete there and the
24 Court of Appeals, had it gone forward without the govern-
25 ment's concession, could have said, "A, we went on the

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2 merits or, B, we are entitled to a hearing or, C, we
3 lose."

4 But it was the government which backed off and
5 said, "We were wrong for the March order," not for lack
6 of notice, that was never raised as to the March order.
7 They didn't say, "We were wrong as to the March order,"
8 they said, "We were wrong as to the control."

9 THE COURT: The errors of FDA are not necessarily
10 determining here, are they? The record may be replete
11 with errors, but does that really resolve the question
12 of --

13 MR. WEIGEL: I think it clearly resolves the
14 issue of whether or not we have established the propriety
15 of those tests on the first issue that now we can't be
16 forced to go back on that same issue, that that has
17 been -- and the only reason it wasn't adjudicated on
18 the merits was because the government frustrated us and
19 the Court by withdrawing it.

20 THE COURT: All right. Please continue.

21 MR. WEIGEL: As we point out in our papers,
22 there still is a very important statutory prerequisite
23 of the new information if they want to proceed on the
24 new ground, the combination theory.

25 Yes, the Court of Appeals said:

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2 "You may proceed, you are not likely to
3 win, however, you must proceed within the terms
4 of the statute and your own regulations."

5 And, they haven't done that. They have no new
6 information.

7 They concede in their brief, which is before
8 you today, that the new information is this NAS-NRC
9 report, which has been the subject of litigation and
10 resolved favorably in plaintiffs' behalf and no way
11 mentions the combination theory. The report quite clearly
12 indicates this is a single entity drug.

13 THE COURT: I am just back to the earlier point
14 reading again here from page 3129, the Court of Appeals
15 stating:

16 "Concedingly erroneous though it was and
17 despite the continuing pendency of the appeal, the
18 March 2nd order is no longer in force and effect.
19 We fail to see what relief could be granted to
20 petitioners under these circumstances. The appeal
21 from the March 2nd, 1973 order must be dismissed
22 as moot."

23 Of interest is the second sentence, "We fail
24 to see what relief could be granted to petitioners under
25 these circumstances."

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2 If I were to adopt your argument that issues
3 presented in these administrative proceedings had been
4 passed upon at the Court of Appeals level and are res
5 judicata, there is relief that has been offered of some
6 kind.

7 MR. WEIGEL: Yes. We had our relief at the
8 time that they withdrew the March order and reinstated
9 our NDAs.

10 In effect, they said:

11 "We concede, after six long years, that
12 you are right, you have adequate and well controlled
13 studies to show the effectiveness of your drug.
14 However, we are going to put in a new order because
15 we have an entirely new theory and we are going to
16 ask you to do some tests you never thought of and
17 we didn't think of until the Supreme Court told
18 us in the instant case we are going to lose."

19 So there was really nothing on that order for
20 the Court of Appeals to do. But I don't believe that the
21 government at that stage of the proceedings can confess
22 judgment, as they did, and it is in the opinion, and give
23 us the relief we want and then come back a few months
24 later and say, "Gee, we would like to litigate it all
25 over again on the same theory."

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THE COURT: All right. Does that complete your presentation, counsel?

MR. WEIGEL: I would like to be heard on our request for a stay.

THE COURT: Why don't I hear from counsel for the agency first and then we will take that up.

MR. WEIGEL: And I assume that at that point, when the Court of Appeals made those statements, they were not thinking in terms of the government proceeding again on a theory ^{on} ~~out~~ of which it confessed error and said they were erroneous and did not want to pursue.

Thank you.

THE COURT: All right.

Mr. Siegel.

MR. SIEGEL: Before I begin my regular presentation, I would just like to point out what seems to me to be a fundamental error in counsel's analysis of the Court of Appeals decision.

The Court of Appeals in describing the agency action as abandonment should not be understood to have found the agency to have actually made a determination on the merits. The Court of Appeals was sort of factually describing what had happened in the sense from the March order to the August order the agency was no longer proceeding

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2 on the same grounds and in that sense had abandoned its
3 theory.

4 By no stretch of the imagination is such a
5 change in theory a determination on the merits.

6 I think it is important to understand that the
7 agency's objections to the Miller-Paez and the Cohen
8 study were of two sorts:

9 One, they felt that these studies were improper
10 studies in the sense that they did not test Alevaire
11 against the proper control, and even if they were the
12 proper studies they had not been conducted properly. There
13 were a host of defects in the studies, not simply that
14 the studies were not the proper studies but that they
15 were not properly conducted. Both these grounds were
16 the basis for the agency's actions to them.

17 Now, when the agency agreed to withdraw that
18 March order, what it was saying was not that, yes, these
19 are the proper studies, we have erred, the agency was
20 saying, "You have raised certain points with respect to
21 our criticisms of the way these studies were conducted
22 and we are going to re-examine our criticisms of those
23 methods."

24 I am quoting here from the brief filed in the
25 Court of Appeals and just as an example of what was involved

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2 here, the March order stated that Dr. Cohen did not state
3 "The diagnostic criteria for identifying bronchial
4 asthma and chronic bronchitis patients."

5 This was a criticism, once again, of the
6 method that was conducted, not the propriety of the
7 tests.

8 What happens is the agency acknowledges that
9 these were true. However, the paper did contain a foot-
10 note to a publication containing diagnostic criteria.
11 These criteria were apparently used to select patients,
12 although it is nowhere explicitly stated in the paper.

13 My point is that the objections of the agency
14 were twofold, one, these were improper studies, two, even
15 if proper they were improperly conducted.

16 To show you or to illustrate the fact that the
17 agency had not, in fact, abandoned its contention that
18 these studies were proper, one only need look to the
19 August order itself. In that order, that is in Plaintiffs'
20 Exhibit 3, page A 545, reading from that order, it says:

21 "Even assuming that the studies are adequate
22 and well controlled investigations comparing Alevaire
23 with other controlled substances, a conclusion not
24 warranted by analysis of the investigations, the
25 studies cannot demonstrate the effectiveness of

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1 Alevaire because their design precludes assess-
2 ments respecting the contribution each of the three
3 components of Alevaire makes to the claimed effect-
4 iveness of the drug."
5

6 My point is that in abandoning this so-called
7 single entity theory, the agency was in no sense conceding
8 and certainly had not made any determination on the
9 merits that the studies done were proper, either the
10 proper studies or properly conducted.

11 You know, this is really the fundamental flaw
12 in counsel's analysis of the Court of Appeals opinion.
13 The order was concededly erroneous because the agency
14 essentially conceded that it had erred in its analysis
15 of the data and was going to reconsider it.

16 If the Court would entertain a perhaps some-
17 what inapposite analogy, it would be like a judge issuing
18 findings of fact and counsel petitions for reconsideration
19 claiming there was an error in the findings of fact and
20 the Court granting that motion and reconsidering. The
21 effective withdrawal of the finding of fact that will
22 occur upon granting that motion would not be a concession
23 that the opposing claims were accepted as findings. This
24 is not a determination.

25 I think this is where counsel is really in error.

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The Court of Appeals opinion was not a decision on the merits. There was no determination by the Court that the studies submitted were, in fact, adequate and well controlled such as to require the holding of a hearing, much less that Alevaire itself was conceded to be effective by the agency.

Looking at the case in its entirety, I think it is important to realize the very extraordinary nature of the relief which the plaintiffs are requesting here.

They are asking this Court to enjoin agency proceedings prior to any final action on the part of that agency and, in effect, without having exhausted their administrative remedies. They have to date submitted no evidence to the agency, none whatsoever, they have raised no legal claims before the agency, both of which are required by the statute and the applicable regulations prior to obtaining judicial review of any agency action.

In sum, they seem to carve out an exception to the exhaustion requirement and they seek to do so on what we would contend is an extremely weak record.

They raise the claim of irreparable injury here, ignoring the fact that preliminary injunction issues only when there is a threat of irreparable injury for which

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2 there is no adequate remedy at law. Here they not only
3 can go to the Court of Appeals to seek a stay of the
4 agency's action when that action and if that action is
5 finally taken, they can go to the agency itself and seek
6 a stay from the agency of its order when and if it issues.

7 This procedure has been followed in the past.
8 The agency has in the past frequently granted such stays
9 of its order pending the taking of an appeal.

10 Although they assert this threat of injury,
11 they ignore the fact that they do, in fact, have several
12 adequate remedies at law.

13 More importantly, I think in cases such as
14 this there is precedent which we have cited in both the
15 American Cyanamide and the Upjohn cases for the proposition
16 that when you are talking about the withdrawal of approval
17 of a drug, aside from the showing or the demonstration that
18 there is a likelihood of irreparable injury for which
19 there is no adequate remedy, the Courts have paid par-
20 ticular attention to the likelihood of prevailing upon
21 the merits, which is a typical showing that has to be
22 made in order to obtain a preliminary injunction, and
23 we contend and we have set out in our briefs the reasons
24 why we feel there is virtually no possibility of success
25 on the merits of this case.

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The Court of Appeals indicated the course which was to be followed in the future; the agency is now doing that. Without getting into an extensive discussion of the merits of the case again, although I do want to return to that, I think it is important to realize that despite allegations of injury where there really is no showing of a reasonable probability of success on the merits, Courts have been loathe to entertain arguments about irreparable injury.

I think another factor to be considered when they talk about their claims of irreparable injury, in a case like this when you are talking about enjoining a public agency are certain public interests which come into play, and I have discussed these in my briefs but would like to bring them to the Court's attention again.

It is really of paramount importance that the public interest in a matter like this be considered. Plaintiffs casually assert, well, there is really no hardship on the agencies, these proceedings have been going on a long time, the drug has been on the market all that time, it is a safe drug so there is really no hardship on the agency in allowing this to remain on the market for a while longer.

We are not only talking about the working of

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2 what amounts to a somewhat of a financial fraud on the
3 public, but we are talking about action by these people
4 which could --

5 THE COURT: You mean potentially?

6 MR. SIEGEL: Yes. Excuse me.

7 -- which could potentially pose a threat to
8 the public health.

9 We don't want to get into speculation about
10 how severe the threat is and we don't really mean to
11 raise strawmen here, but as I understand it Alevaire
12 is normally administered to people with respiratory diseases
13 and particularly through things like oxygen tents. Very
14 often those people need, you know, extremely effective
15 medication. You are talking about a mucosolvan of
16 mucus from the lungs.

17 The point really is that if the product really
18 is ineffective people are relying on it to cure serious
19 illnesses. If it is ineffective, they are both lulled
20 and improperly treated as a result of the drug remaining
21 on the market.

22 I would refer the Court's attention again to
23 the several references to this problem in the Congressional
24 record in the Senate report considered by Congress when
25 the 1962 amendments were on the floor of the Congress.

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The point is simply that there are very grave public concerns about health involved here and when those are thrown into the balance we think even aside from the lack of probability of success on the merits there is strong reason not to issue an injunction in this case.

Turning to the merits briefly, I think it is incumbent to point out again that both the claims asserted here really are based on a res judicata theory and they both suffer from the same fundamental flaw, namely, that there has, in fact, never been any prior determination on the merits either that Alevaire was effective or that the tests submitted were adequate, either as to the controls being adequate or as to the way they were being conducted. The Court of Appeals clearly did not make a determination on the merits. That dealt with the fixed-combination ground and that only. The agency has never bent on its position, as I pointed out, and has never actually made a determination on the merits of that decision and no res judicata effect can arise thereby.

This is really the point of the Court of Appeals decision and the real flaw in what plaintiffs continue to argue here.

Their new evidence argument is really based on a similar argument. They are claiming that the NAS-NRC

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2 study, although it was new evidence, can no longer be

3 new evidence because it was used in a prior agency pro-

4 ceeding and was the basis of a decision on the merits

5 specious. Once again, we submit there has been no

6 decision on the merits and, therefore, the claim is

7 ~~unavailing~~ There was no decision on the merits and,

8 therefore, they are not barred from using the studies again.

9 In conclusion, I think it important just to

10 bear in mind that where Congress has provided a statutory

11 system of agency review and judicial review of the

12 agency action, Courts should be cautious in interfering

13 with the agency process by either stay or injunction.

14 I refer the Court to the Supreme Court's

15 decision in Samson versus Murphy for a general discussion

16 of that problem in the context of the dismissal of

17 federal employees. That is at 415 U.S. 61.

18 I point out in this case there really has not

19 been an effort to submit evidence to the agency following

20 the August notice. The agency, for the various procedural

21 errors made in the past, has, as I set out in the brief,

22 attempted over these years to get plaintiffs to conduct

23 one simple service of tests to test their product,

24 the so-called active ingredient tyloxapol, against the

25 vehicle.

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The point is simply that unless you do that there is no assurance that tyloxapol does anything. It could be simply that the water, glycerin and sodium bicarbonate solution -- whatever effect is achieved is achieved by that and that alone and that tyloxapol is ineffective in and of itself.

Despite the agency's attempts over these years, as indicated by the various notices published in the Federal Register, each setting out what was supposed to be done --

THE COURT: It is really not my business, but suppose it should develop that tyloxapol is not the effective ingredient and that it is really the glycerin and the bicarbonate and the water, what difference does it make if it is effective?

MR. SIEGEL: Initially, the statute speaks in terms of effectiveness in terms of the drug doing that which the label says it will do.

THE COURT: Assume it does what the label says, but it is not attributable to the tyloxapol? If the safety factor has been covered, what difference does it make what substance it is that is achieving the desired result?

MR. SIEGEL: It wouldn't matter if the label

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2 didn't make any claims that tyloxapol was an active
3 ingredient.

4 THE COURT: You mean just acknowledging that
5 it is present in the mixture?

6 MR. SIEGEL: Pardon?

7 THE COURT: You would find it satisfactory
8 that it was acknowledged that present?

9 MR. SIEGEL: I don't think there would be
10 any problem with acknowledgment of its presence, it is
11 just any claim for activity made on the part of tyloxapol
12 that is objected to.

13 THE COURT: All right. Anything further?

14 MR. WEIGEL: Yes, if I may, please, briefly,
15 your Honor.

16 Of course, this is the first time in six
17 years we have had any indication that there was a problem
18 of the public interest involved. I think the record in
19 the Court of Appeals indicates from all of the experts
20 in this country that this is an effective drug and the
21 most effective drug available today for the purposes for
22 which it is offered.

23 The matter of no abandonment has come up,
24 your Honor, and I must point out that in my affidavit in
25 Paragraph 13 of my affidavit that was filed on this motion

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I have stated unequivocally under oath that in the Court of Appeals that counsel for the defendant stated that the FDA no longer objected to the Miller-Paez and Cohen studies as being inadequate or uncontrolled, but only argued that they were unresponsive on the new fixed-combination theory.

I have with me three colleagues, members of the Bar who were present at the time, and are in a position to establish the same fact.

I don't believe if that were not the intention of the government it would have made the statement which has been quoted in the Court of Appeals decision that: "We fail to see what can be granted to petitioner --"

Wait a minute. This is the statement on page 3129.

"We again confess error with the hope that petitioners will not look a gift horse in the mouth a second time."

Certainly that statement would not have been made by the government nor made by the Court of Appeals if we were to be faced again in a new proceeding with the very same issue. In effect, they told us, "You won on that issue, take what you have and run with it because we have a new theory to try out on you."

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2 I don't think, your Honor, that an agency can
3 keep issuing and withdrawing orders, making them moot,
4 avoiding any sort of judicial review and trying to avoid
5 the effect of collateral estoppel. The government has
6 abandoned its prior orders and I think it clearly should
7 be enjoined from trying to re-litigate them again at
8 this time.

9 They say, "Oh, we haven't exhausted our
10 administrative procedure."

11 We have for six long years. We are not trying
12 to ask for any special exception from that doctrine. I
13 don't know how else one raises res judicata other than to
14 proceed the way we have. We should not be subjected to
15 an illegal action or an improper action and be told
16 maybe six years from today, "Well, the government shouldn't
17 have proceeded that way."

18 Your Honor, I do believe that we are quite
19 clearly entitled to the relief we seek and preliminarily on
20 this motion. There has clearly been final action, there
21 has been an acknowledgment that the drug is an effective
22 drug. We have litigated the issue whether or not we
23 should have tested it against its vehicle or whether the
24 control which was suggested to us by NAS and FDA was a
25 proper one. We did what they asked us to do back in 1968.

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2 They said, "Test this against water or saline and show us
3 that it is more effective," and we did that very thing
4 and I don't think we should now have them say, "We have
5 a lot of new tests we would like you to perform," when
6 you have a clearly safe and effective drug.

7 Your Honor, it was pointed out by Mr. Siegel
8 that we have not submitted any materials under the
9 August 1974 order. No, we have not. We are not required
10 to do so until next Tuesday, and it is for that reason
11 we have asked for a stay. We don't feel that until
12 this issue has been resolved that we should, in effect,
13 be forced to go through this illegal procedure and we
14 respectfully request a stay of thirty days. It will take
15 a good thirty days to assemble our materials after you
16 have ruled on the motion for preliminary injunction.

17 Thank you.

18 THE COURT: You are asking for thirty days
19 from when?

20 MR. WEIGEL: From the time when you might rule
21 on our motion for preliminary injunction, the motion which
22 is before you today, if it is adverse. If we are denied
23 our motion and are told that we must go forward and
24 subject ourselves to the administrative proceedings, we
25 would like thirty days at least to file our information

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2 with the government.

3 THE COURT: I am given to understand that the
4 FDA has some constraints imposed upon it by another
5 district court which --

6 MR. WEIGEL: Your Honor, they have raised the
7 question of Judge Bryant's order in the Vennaman case
8 which really has no relevance here at all. That decision
9 by Judge Br^{yn}iant down in the District of Columbia said
10 in effect, "Publish these NAS-NRC reports and start to
11 implement them."

12 For a long time the Food and Drug Administration
13 was receiving the reports from the NAS-NRC and doing
14 nothing about them. They have published the Alevaire, ^{Report}
15 they have started to implement it, they have certainly
16 complied with Judge Bryant's order in this instance and
17 in any event that order is not certainly binding upon you
18 here in a litigated case. They are not operating under
19 any restraints as far as granting an extension of time.

20 Granted, the medical director of the Food
21 and Drug said that is how he interpreted that when he
22 denied our request for extension. I don't believe that
23 that is binding in any way upon this Court and it is not
24 relevant to a proceeding that has already been instituted.

25 THE COURT: Counsel?

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MR. SIEGEL: We would oppose the stay for several reasons.

First of all, just to refer the Court to page 6 of Judge Bryant's order, Paragraph X, it specifically states, "The defendant shall not grant any extension of time for any request for a hearing or other response or a notice of opportunity for hearing."

THE COURT: That really isn't the problem here, because you are not being asked to grant an extension.

MR. SIEGEL: That's correct. The request for a stay is being addressed to the Court, not to the agency.

THE COURT: Yes.

MR. SIEGEL: With respect to that, I want to say several things.

One, it should be recognized that they have now had some fifty days from the issuance of the order --

THE COURT: Let me interrupt for a minute and maybe cut through all of this.

What is the stay you would ask?

MR. SWIRE: We have a formal order.

THE COURT: May I see it?

Have you seen it?

MR. SIEGEL: No.

MR. SWIRE: We will pass a copy back.

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2 MR. WEIGEL: I might say the government has not
3 felt itself precluded by Judge Bryant's order to have
4 granted stays in the past in this very case.

5 MR. SIEGEL: From withdrawals of orders, not
6 from notices.

7 One point, your Honor. I think if the Court
8 were convinced that it lacked jurisdiction over this
9 matter, I think it important to point out that the
10 All Writs Act provides that the Court's can issue such
11 stays as are necessary and appropriate in aid of their
12 respective jurisdictions.

13 If this Court, in fact, lacks jurisdiction
14 over this matter, I would submit that no stay would be
15 appropriate in this case.

16 THE COURT: Except we are not going to find out
17 whether this Court lacks jurisdiction this soon, are we?

18 Where do I have authority from to grant a thirty-
19 day stay?

20 MR. SWIRE: Excuse me, your Honor. This is
21 not under the temporary restraining order provisions,
22 this is under the All Writs Act.

23 THE COURT: I see.

24 Mr. Siegel, I am going to take all of this
25 under advisement, including the application for a stay.

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2 I will get out something on this stay question one way
3 or the other I suppose today.

4 I must say that my inclination is, having con-
5 sidered Judge Bryant's position and giving it respectful
6 attention and recognizing that the restraint which he
7 sought to impose there was upon the agency and recognizing
8 that while that has some persuasive effect here, it
9 really doesn't solve the problems presented to me once an
10 issue is laid before me as a district judge.

11 My inclination is to grant the stay principally
12 because of the zig-zag patter which has been followed in
13 this case over this period of time, a back and forth
14 pattern, which I think the government cannot deny has
15 existed given the history of the case, on again, off
16 again.

17 MR. SIEGEL: This would be a stay of withdrawal
18 order in order that plaintiff could submit evidence to
19 the agency?

20 THE COURT: I understand you to be asking simply
21 for additional time to meet that requirement.

22 MR. WEIGEL: Yes, your Honor.

23 THE COURT: Are we all talking about the
24 same thing?

25 MR. SWIRE: In the event of an adverse decision

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2 on the preliminary injunction.

3 THE COURT: In the event of an adverse decision.

4 All right, decision is reserved on the appli-
5 cation is here. However, let me say that I want you to
6 submit proposed findings of fact and conclusions of law
7 by Friday, October 11, at 10:00 a.m. in chambers.

8 Is there anything further?

9 MR. WEIGEL: Yes.

10 MR. SIEGEL: Your Honor, might I make one
11 suggestion?

12 THE COURT: Yes, sir.

13 MR. SIEGEL: If it were ultimately determined
14 that, in fact, the Court lacked jurisdiction, I would
15 think that the stay itself would be vacated at that
16 point.

17 A more useful course might be to reconvene in
18 a week's time, in order, just prior to the withdrawal order
19 becoming effective, and if at that time the Court were
20 inclined to find that it did have jurisdiction or it
21 did not, it could then consider the appropriate necessity
22 of entering a stay.

23 MR. SWIRE: We are past that.

24 THE COURT: One problem is I am going to be
25 in Washington at the Federal Judicial Center for about

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2 a week.

3 MR. SWIRE: The further problem is we would
4 be past our time by that point.

5 THE COURT: And their time ends October 15th,
6 doesn't it?

7 MR. SWIRE: Yes.

8 [THE COURT: What I would like to see happen
9 here is that I have the opportunity, as I expect I have,
10 to pass on the request for relief which has been argued
11 here today and that the stay aspect be the one which
12 is carried out just on the basis of basic fairness.
13 Let them have the opportunity, if it gets to that point,
14 let them have the opportunity to have their thirty days,
15 especially given the past history of this case.

16 I am suggesting it to you very strongly. If
17 I may say so, I just don't think the agency is in a
18 position to take a hard line on this question given the
19 history of the case.

20 You step back and take a look at it from a
21 non-party standpoint of view and I think you will come
22 to the same conclusion. So why don't you give it some
23 consideration in terms of tolerating it if it occurs, not-
24 withstanding all of the reasons why you may think for the
25 moment it shouldn't occur.

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2 Mainly, I want to get to the principal issue
3 that has been presented here and I want to make sure they
4 have some sense that ^{they have the sense that} is necessary for them to present
5 their case. All right?

6 MR. SIEGEL: You want the proposed finding
7 of facts?

8 THE COURT: Yes. Give me the proposed
9 findings of fact and the conclusions of law by the 11th,
10 10:00 a.m.

11 MR. WEIGEL: Your Honor, before the record
12 is closed, I would like to reiterate my offer to have
13 three live witnesses to the fact that the government did
14 in open court in the Court of Appeals in response to ques-
15 tioning by the Court abandoned any objections it had to
16 the adequacy or the controls of those studies, as I
17 have stated in my affidavit.

18 Thank you.

19 THE COURT: Is counsel for the agency prepared
20 to concede that if these three live witnesses were called
21 to testify that they would testify as counsel has indi-
22 cated without conceding the truth thereafter? ^{of}

23 MR. SIEGEL: Yes, your Honor.

24 THE COURT: All right. Decision is reserved.

25 oOo

OPINION NO. 41,381
A. 197

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

STERLING DRUG, INC., WINTHROP
PHARMACEUTICALS, INC. and ERECH
LABORATORIES, INC.,

Plaintiffs,

- v -

CASPAR W. WEINBERGER, Secretary
of Health, Education and Welfare,
and ALEXANDER M. SCHMIDT,
Commissioner of Food and Drugs,

Defendants.

74 Civ. 4282

Opinion # 41381

PIERCE
Rm. 514

Filed
Oct. 21, 1994

APPEARANCES:

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LAWRENCE W. PIERCE, D.J.

MEMORANDUM OPINION

The plaintiffs herein, manufacturers and distributors of the prescription drug Alveaire, seek to enjoin the defendants from proceeding to withdraw approval of the New Drug Applications (NDA's) now in effect for Alveaire. Oral argument was heard on this matter on October 10, 1974 at which time the application was consolidated with trial on the merits pursuant to Rule 65 of the Fed.R.Civ.P.

Plaintiffs Sterling Drug, Inc. and Winthrop Products, Inc., a subsidiary of Sterling, are Delaware corporations and the holders of the NDA's. Plaintiff Breen Laboratories, Inc., also a subsidiary of Sterling, is a New York corporation responsible for the marketing of the drug in the United States. Defendants Weinberger and Schmidt are the Secretary of Health, Education and Welfare and the Commissioner of the Food and Drug Administration (FDA), respectively.

The general background of this litigation is not in dispute. Alveaire is an aerosol prescription drug composed of 0.125% tylozapol, 2% sodium bicarbonate, 5% glycerine and 92.875% water. It is administered to patients with obstructive lung conditions to aid in the evacuation of broncho-pulmonary

secretions. It appears that NDA's for Alevalire were approved by the FDA in 1952. At that time under the controlling statute, that is, the Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. §301 et seq., only the safety factor was considered. In 1962 the Act was amended to allow the FDA to remove from the market drugs with approved NDA's if substantial evidence was lacking that the drug was effective for its intended use. To comply with this legislative mandate, the FDA retained the National Academy of Sciences-National Research Council (NAS-NRC) to review the effectiveness of each drug which had been approved up until then. Such a study was undertaken of Alevalire and the NAS-NRC concluded that the drug was ineffective for its intended use. By notice published in the Federal Register of July 17, 1968 (33 Fed. Reg. 10227) the FDA announced that it concurred with this evaluation.

Pursuant to 21 U.S.C. §355(e) the FDA published on December 6, 1969 a "Notice of Opportunity for Hearing" in the Federal Register indicating its intention to withdraw its approval of the drug. Apparently it based its conclusion that the drug was ineffective primarily on the criticism of the NAS-NRC that Alevalire was no more effective than water. To refute this finding and to support their request for a hearing^{1/} the plaintiffs submitted two studies--the Miller-Paez

Study and the Cohen Study. The former study compared the drug with water and saline and the latter compared it with water alone. Both studies concluded that Alevaire was an effective mucocoughant.

On August 27, 1971 the FDA found that these studies were not "adequate and well controlled" within the meaning of 21 C.F.R. §130.12(a)(5)(11)(1973) and accordingly denied the request for a hearing. Simultaneously the FDA withdrew its approval of the drug. Thereafter the plaintiffs appealed to the court of appeals pursuant to 21 U.S.C. §355(h). While the appeal was pending in the Second Circuit, the FDA terminated its August 27 order and moved in the court of appeals to remand the case to the FDA for further administrative action. The motion to remand was granted on January 11, 1972.

On March 2, 1973 the FDA issued a second order again denying the request for a hearing and withdrawing approval of the drug on the ground that the Miller-Paez and Cohen Studies were not "adequate and well-controlled". This time, however, the FDA indicated that water was not the proper "control" with which to compare the effectiveness of Alevaire. Instead, the proper "control" was said to be Alevaire minus tyloxapol, that is, Alevaire's vehicle solution of 2% sodium bicarbonate, 5% glycerine and 93% water.^{2/}

The plaintiffs then petitioned the FDA to reconsider its March 2 order and also appealed to the Second Circuit seeking to have the order set aside. On June 14, 1973 the FDA terminated the March 2 order and reinstated approval of the NDA's for Alovaire. It also moved to dismiss the appeal from the March 2 order.

While a decision on its motion before the court of appeals was pending the FDA on August 7, 1973 again issued another order denying the petition for a hearing and again withdrawing approval of the drug. However, this time the FDA claimed that Alovaire was a "fixed-combination" drug within the meaning of 21 C.F.R. §3.26 (1974). Accordingly, the FDA maintained that, in order to support the effectiveness of the drug, studies had to be made assessing the contribution each of the three components of Alovaire made to the claimed effectiveness of the drug. Since the Miller-Poon and Cohen Studies were not addressed to this theory, they were rejected as irrelevant. The plaintiffs again appealed to the Second Circuit seeking to set aside the August 7 order.

The appeals from the March 2 and August 7 orders were consolidated (after the FDA's motion to dismiss the appeal from the March 2 order had been denied) and on May 2, 1974

the Second Circuit rendered its decision. It dismissed the appeal from the March 2 order as moot and it set aside the August 7 order because the plaintiffs had not been initially notified of the grounds on which the approval of the NDA's was ultimately withdrawn by that order. Accordingly, the Court reinstated approval of Alevaire.

On August 13, 1974 the FDA published in the Federal Register a new "Notice of Opportunity for a Hearing" indicating its intention to withdraw approval of the drug on two alternative theories: (1) treating Alevaire as a single entity drug the FDA maintained that it had to be compared with its own vehicle, that is, Alevaire minus tyloxapol; (2) treating Alevaire as a fixed combination drug, the FDA contended that Alevaire's effectiveness had to be tested by comparing the effectiveness of each of its components. The plaintiffs were given until September 12, 1974 to file a notice of appearance and request for a hearing and until October 14, 1974 to furnish the FDA with the necessary information supporting the request for a hearing. On August 15, 1974 the plaintiffs sought to have their time extended but this request was denied. On September 10, 1974 the plaintiffs requested a hearing on this matter; however the data to support this request has not yet been provided to FDA.^{3/}

OPINION NO. 41,381
A. 203

On September 30, 1974 plaintiffs filed the complaint herein and the application for a preliminary injunction was brought on by an order to show cause dated October 1, 1974. As noted the application was consolidated with trial on the merits and oral argument was held on October 10, 1974. The parties incorporated all the documents submitted to the Court as part of the record in the case.

The plaintiffs attack the legality of the administrative proceedings on two main grounds. First, they allege that the defendants are barred by the doctrines of res judicata or collateral estoppel from maintaining that the effectiveness of Alcovaire can only be demonstrated by comparing it to its vehicle. In their view, the May 2, 1974 Second Circuit decision rejected the validity of this contention and accordingly the defendants may not again proceed against plaintiffs on the basis that the proper "control" with which to compare Alcovaire is Alcovaire minus tylenapol. Alternatively, the plaintiffs claim that the defendants may not now proceed on this theory since they explicitly abandoned it in briefs submitted to and oral argument before the Second Circuit. Secondly, the plaintiffs argue that the defendants may not treat Alcovaire as a fixed combination drug since it lacks the "new information" required by 21 U.S.C. §355(c)(3).

The Court has concluded that it need not reach the merits of the plaintiffs' arguments since in its view the complaint herein must be dismissed for failure to exhaust administrative remedies.

Subject to certain exceptions it is settled that a federal district court may not review interlocutory administrative decisions. McKart v. United States, 395 U.S. 185 (1969); Boira v. Greyhound Corp., 376 U.S. 473 (1964); Hyman v. Rothblum Shipbuilding Corp., 303 U.S. 41 (1933). In this case the proposed withdrawal of approval for the NDA's is admittedly not a final order and hence not ordinarily reviewable in the district court. In fact any review of FDA action concerning withdrawal of an NDA normally is to be made by the court of appeals pursuant to 21 U.S.C. 355(h). As another court has stated: "[W]here Congress has provided an adequate procedure for judicial review of administrative action, that procedure must be followed. Only in extraordinary cases will parties be allowed to deviate from this statutory course and seek injunctive relief from the district court, short-circuiting the administrative procedures." Coca-Cola Co. v. FTC, 342 F. Supp. 670, 675 (N.D. Ga. 1972), aff'd, 475 F.2d 299 (5th Cir.), cert. denied, 414 U.S. 877 (1973).

The plaintiffs have argued that the exhaustion doctrine is inapplicable here because "[b]oth by attempting to relitigate previously decided matters and in proceeding without the requisite statutory base [that is, without the required "new information"], defendants are proceeding in violation of law." Reply Memorandum at 10. In this Court's view this argument is not well taken since its adoption would undercut the very rationale of the exhaustion doctrine. Perforce the claim in every suit of this type is that the administrative agency is acting illegally. If a court without more were to rule on the merits of each such claim this would undermine basic administrative law procedures and thereby promote the very piecemeal litigation which the doctrine in part aims to discourage.

Admittedly the plaintiffs are not foreclosed from raising their res judicata defense on an appeal from whatever adverse final determination the agency may make. Faced with this the plaintiffs contend that it would be a "total perversion" of the doctrines of res judicata and collateral estoppel to compel them "to relitigate previously decided matters and then argue res judicata on appeal only." Reply Memorandum at 10. However, both reason and authority, in this Court's judgment, are contrary to the plaintiffs' position.

In an analogous situation, a denial of a motion to dismiss a complaint on the ground of res judicata has been held not to be immediately appealable. Patko v. Eshely, 353 F.2d 511 (3d Cir. 1965). Such a result is not at all viewed as a "total perversion" of the doctrine. Similarly, here, had plaintiffs first presented the res judicata argument before the FDA and had it been rejected there, this Court does not believe that plaintiffs could have then immediately appealed this determination to the court of appeals. They should not be permitted to avoid this result simply by sidestepping agency consideration and raising their defense directly before a district court. Instead, the proper procedure is for the plaintiffs to raise this defense in the administrative proceedings and then have the agency determination on this issue (should it be contrary to plaintiffs' claim) reviewed on the appeal to the court of appeals from whatever adverse final decision the FDA may make with respect to the withdrawal proceedings.

The Court is not insensitive to the real possibility that this procedure may compel the plaintiffs to expend additional time, money and effort in further contesting the withdrawal proposal. Nevertheless, the Court feels that such a possibility is an insufficient basis for allowing the plaintiffs

to circumvent the proper administrative channels. See Williamson v. United States, 261 F.Supp. 503, 520 (S.D.N.Y. 1966).

Moreover, the Supreme Court has required exhaustion of administrative remedies in spite of a claim that a proposed administrative investigation was barred by res judicata. SEC v. Galt & Co., 333 U.S. 243 (1949) (per curiam). Galt & Co. v. SEC, 176 F.2d 24 (D.C. Cir. 1949). Galt & Co. stands for the proposition that a claim of res judicata is insufficient to support an injunction of proposed administrative action. See Gann-Gula Co. v. FTC, 475 F.2d 299, 304 (5th Cir.), cert. denied, 414 U.S. 877 (1973). Accordingly, plaintiffs' res judicata defense must first be disposed of through administrative channels.

As noted above as a second ground for their application plaintiffs argue that the agency is proceeding without "new information" as required by 21 U.S.C. §355(c)(3). This statute requires that the Secretary ^{6/} withdraw approval of any application if he finds "on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence" of effectiveness. In the plaintiffs' view, the agency does not have any such

"new information" to support its conclusion that Alcovaire may be treated as a fixed-combination drug.

Whether the agency does in fact possess "new information" to support its conclusion is a factual determination which should first be made by the FDA. Contrary to plaintiffs' argument this issue does not present a straightforward question of statutory construction as in Jewel Corporation, Inc. v. FTC, 432 F.2d 1135 (7th Cir. 1970). It is incontrovertible that the FDA has before it reports and other data dealing with the effectiveness of Alcovaire. Whether an assessment of this data will justify treatment of the drug as a fixed-combination drug is a question which should first be decided by the FDA. Only after this determination is made and it then becomes clear on what specific information the agency has relied for its conclusion can a Court determine whether the data used constitutes "new information" within the meaning of the statute. It may well be, as the Second Circuit observed, that there may be "little in the record . . . to support the proposition that Alcovaire is a fixed combination drug." Stearns Drug, Inc. et al. v. Weinberger et al., Civil Nos. 73-1523 and 73-2481 at 3137 (2d Cir., May 2, 1974). Nevertheless, the FDA should first

be given the opportunity to decide the question "on a full and proper record". Id. Plaintiffs, of course, have the right to appeal to the court of appeals from an adverse determination.^{5/}

The plaintiffs' application for an injunction is denied and the complaint is dismissed.^{6/}

The foregoing shall constitute this Court's findings of fact and conclusions of law pursuant to Rule 52(a) of the Fed.R.Civ.P.

Submit order on two days notice.

SO ORDERED.

Dated: New York, New York
October 31, 1974

LAWRENCE W. PIERCE
U. S. D. J.

FOOTNOTES

1. 21 C.F.R. §130.14(b) (1973) provides, *inter alia*, that a request for a hearing must be accompanied by "a well-organized and full factual analysis of the clinical and other investigational data" the applicant is prepared to prove at such a hearing. The request "must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact . . . , e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness," the Commissioner may deny a hearing and enter an order withdrawing the application based solely on these data.
2. Prior to this time the FDA had indicated that either water or Alevalire minus tyloxapol would be a proper "control".
3. By stipulation it was agreed that plaintiffs would have 15 days from the filing of this decision to submit to the FDA the necessary data in support of the request for a hearing.
4. The Secretary of Health, Education and Welfare has delegated his responsibilities under the Federal Food, Drug and Cosmetic Act to the Commissioner of Food and Drugs. 21 C.F.R. §2.120 (1974).
5. In this connection the Court finds somewhat puzzling the plaintiffs' contention that on appeal the issue of whether the agency has "new information" to support its conclusion would be lost. They premise this argument on the assertion that if they are forced through a hearing the agency can somehow "create" this new information "after the fact". The Court fails to see how the agency can manufacture information which it simply does not have.

FOOTNOTES (Cont.)

6. Cases cited by the plaintiffs in support of their position that exhaustion is not required have been examined by this Court and found to be distinguishable. Thus, in Loftin v. Egan, 358 U.S. 184 (1953), the agency action clearly and admittedly violated express statutory standards. In Eino Division of Ewing Co. v. Egan, 343 F.2d 342 (D.C. Cir. 1965), the Court found that relief in the district court was the only effective remedy. Those situations do not exist here. Finally, Fay v. Bouda, 173 F.2d 720 (2d Cir. 1949), is also inapposite. There a strong showing was made that the agency action violated the constitutional rights of the plaintiff. See Harmon v. FCC, 343 F.Supp. 396, 399 (S.D.N.Y.), aff'd, 472 F.2d 179 (2d Cir. 1972), cert. denied, 416 U.S. 876 (1973). Such is not the case here.

JLS:mb
d-332

DEFENDANT'S POST-TRIAL MEMORANDUM
A. 212

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

STERLING DRUG INC., WINTHROP
PRODUCTS, INC. and BERON
LABORATORIES, INC.

Plaintiff : DEFENDANT'S MEMORANDUM

-v-

: 74 Civ. 4232 (LWP)

CASPAR W. WEINBERGER, Secretary
of Health, Education and Welfare,
Commissioner of Food and Drugs,

Defendants. :

MEMORANDUM

- At the conclusion of the trial proceedings on October 10, 1974, there was left unresolved a question concerning certain concessions claimed to have been made by counsel for defendants before the Court of Appeals in February of 1974. Having spoken with counsel at those proceedings, the government is prepared to submit at the present time affidavits in support of the position directly contrary to that of Mr. Weigel's affidavit and the statements he made at the proceedings on October 10.

More simply, however, the government has determined that the tape recording of that argument before the Court of Appeals still exist and is presently making application to the Court of Appeals for permission to hear

DEFENDANT'S POST-TRIAL MEMORANDUM

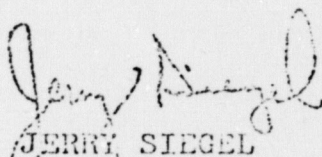
A. 213

JMS:mb
d-332

those tapes. However, since the tapes do exist, the government would suggest that if the matter is of concern to the court, it may wish to hear the tapes itself.

Respectfully submitted,

PAUL J. CURRAN
United States Attorney For the
Southern District of New York
Attorney for Defendant



JERRY SIEGEL
Assistant United States Attorney

- Of Counsel-

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 214

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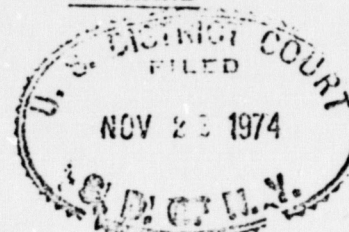
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October 15, 1974

Honorable Lawrence W. Pierce
United States District Judge
United States Courthouse
Foley Square
New York, New York 10007

BY HAND



Re: Sterling Drug Inc., et al. v. Caspar W. Weinberger,
et ano., 74 Civ. 4282 (LWP)

Dear Judge Pierce:

We are in receipt of the memorandum filed by counsel for defendants in this action concerning the concessions made by the defendants' attorney, Robert Allen, on oral argument in the Court of Appeals in the case decided by that Court on May 2, 1974.

We note at the outset that counsel for defendants were well aware that plaintiffs would rely on the concessions made by the defendants throughout the course of this proceeding, including but not limited to the concession in open court referred to above. Mr. Allen's colleague in Washington, Howard Epstein, as well as the U. S. Attorney, had been served with all of plaintiffs' moving papers, including my affidavit, prior to the filing of defendants' reply affidavits and memoranda. Mr. Epstein had also been present in the Court of Appeals, yet neither he nor Mr. Allen chose to offer any rebuttal to the specific statement made in paragraph 13 of my moving affidavit.

Since defendants would now supplement the record after hearing, we take the liberty of enclosing copies of letters which were sent to the Court of Appeals after oral argument. On February 12, 1974 Mr. Allen wrote to the Court of Appeals, concerning the Hess & Clark case. On February 20, we replied and stated, "Since respondents, through counsel, have also conceded

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 215

ROGERS HOGE & HILLS

Honorable Lawrence W. Pierce
Page Two
October 15, 1974

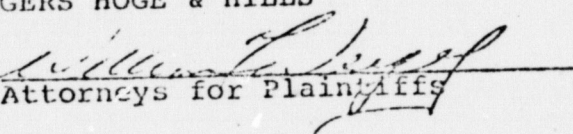
that petitioners' studies are adequate and well-controlled, Alevaire's effectiveness is established and unrebutted." (p. 2). On April 24, defendants' counsel again wrote the Court of Appeals, but nowhere challenged the accuracy of our statement.

Accordingly, we suggest that if defendants have any affidavits to support the statement belatedly made in their latest memorandum, such affidavits should be filed immediately. After such affidavits are received, if the Court then desires, we suggest that counsel jointly listen to the tape of the Court of Appeals argument and prepare and stipulate as to the accuracy of the entire transcript, which may then be submitted to this Court.

As we have already told Mr. Siegel, we think it inappropriate for defendants to listen to the tape prior to filing affidavits, or to listen to the tape without our being present.

Respectfully submitted,

ROGERS HOGE & HILLS

By 
Attorneys for Plaintiffs

WFW:as
Enclosures
cc: Paul Curran, Esq.
United States Attorney

Jerry Siegel, Esq.
Assistant United States Attorney

PL. REPLY TO DEF. POST-TRIAL MEMO

A. 216

FEB 12 1974

RVA
21-51-580

Honorable Daniel Fusaro
Clerk
United States Court of Appeals
United States Courthouse
Foley Square
New York, New York 10007

Re: Sterling Drug, Inc., et al. v. Weinberger,
et al., 73-1628, 73-2481.

Dear Mr. Fusaro:

Pursuant to the Court's permission, granted during oral argument on February 1, 1974, respondents submit this response to petitioners' letter of January 29, 1974.

A.

In paragraph "1" of petitioners' letter, it is argued that the Moss and Clark opinion "reaffirms and further explicates the holding in USV Pharmaceutical Corp. v. Secretary of Health, Education and Welfare, 466 F.2d 455 (D.C. Cir. 1972)." There is one essential difference between the USV case and every other case which arose under the Drug Efficacy Study Implementation (DESI) review program, including the case at bar. In all these cases except USV the Commissioner, in his order denying a hearing and withdrawing the NDA, had thoroughly analyzed all of the data and information submitted by the NDA holder as part of the request for hearing, and he had published detailed findings on the inadequacy of such data and information when held up against the statutory criterion of "substantial evidence" (21 U.S.C. 335(d)) as elucidated in the regulations defining adequate and well-controlled clinical investigations (21 CFR 130.12(a)(5)). In USV the Commissioner had published a final order withdrawing the NDA and denying a hearing with no analysis or findings whatever with respect to the data and information submitted with the

PL. REPLY TO DEF. POST-TRIAL MEMO

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request for a hearing. The court ruled in that case that such a procedure was improper. The Commissioner agreed, and has not followed that procedure in any subsequent case, including the case at bar.

The court stated in Hess and Clark v. FDA, No. 73-1581 (D.C. Cir. January 24, 1974) that "[b]ecause of the context," it did "not explicitly reach in USV the relationship between 'adequate notice' and the Commissioner's pre-summary judgment burden." (slip opinion p. 14) The Court goes on to say that its decision in USV is nevertheless applicable to the issue of "due notice and opportunity for hearing" presented in Hess and Clark. However, as will be shown below, the notice question faced by the court in Hess and Clark, in a safety withdrawal, is quite different from the one presented in the case at bar, involving an efficacy withdrawal, a fact explicitly recognized by the Hess and Clark Court.

B.

The Hess and Clark case arose under the safety provisions of the Act, not the effectiveness provisions, and did not result from the HAS-NRC review implementing the Drug Amendments of 1962. This was clearly understood by the court, and the court's decision explicitly referred to this distinction.

In Hess and Clark, the Commissioner issued a notice of opportunity for hearing, bringing into question the safety of the drug involved (diethylstilbestrol) and then withdrew the drug and denied a hearing on the basis of completely new information. The information was not in existence at the time of the Notice of Opportunity for Hearing and thus the NADA holders had no opportunity to comment. The court held that withdrawal of the NADAs in that manner was improper. The government's present view is that the decision will not be contested although the time for appeal has not yet expired.

In arriving at its decision, the court explicitly discussed its earlier USV holding and the relationship of that decision to the subsequent Hynson decision in the Supreme Court (slip op. 13-16). The court recognized that

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 218

"...it may be that in some particulars the application of USV must be refined in the light of Hynson. In Hynson the Supreme Court approved the FDA's summary judgment procedure permitting withdrawal of an NDA without a hearing if the manufacturer failed to produce 'substantial evidence' of efficacy." (slip op. 15.)

The court then went on to state that, where the agency has issued regulations defining the "substantial evidence" required by the statute, the present FDA form of notice of opportunity for hearing satisfies the requirements of due process:

"Hynson in effect reaffirms the propriety of administrative summary judgment, if taken in a context where the pleadings on their face "conclusively" show that the hearing can serve no useful purpose. It did not overturn USV's requirement that the agency make some showing as a predicate for summary adjudication. It rather found that such a showing and predicate was supplied by particularized regulations setting forth precisely what the manufacturer was required to supply and by findings that the study adduced was conclusively deficient."

Finally, the court recognized that it was "in no way suggesting that the FDA's course must or should be the same regardless whether the ultimate issue is efficacy or safety." (slip op. 16.)

Thus, it is apparent that the United States Court of Appeals for the District of Columbia Circuit has itself recognized that its earlier USV opinion must be "refined" in light of Hynson, and that the form of notice consistently used by FDA to implement the Drug Amendments of 1962 meets all statutory and constitutional requirements.^{1/}

^{1/} Subsequent to the Hynson decision, two other cases have upheld the validity of FDA's NDA withdrawal procedure. Agri-Tech, Inc. v. Richardson, 482 F.2d 1146 (8th Cir. 1973); North American Pharmaceutical, Inc. v. Department of HEW, No. 73-1386 (8th Cir. December 28, 1973). Both decisions rejected legal challenges to the FDA procedure and upheld the contested orders.

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C.

In paragraph "3" of their letter the petitioners argue that the rationale of Hess and Clark when applied to the case at bar would prohibit the Commissioner from using the summary judgment procedure given the type of notice issued by the Commissioner. If this is a correct application of the Hess and Clark opinion to the present case, an efficacy case, it is in direct conflict with this Court's decision in Ciba-Geigy v. Richardson, 446 F.2d 466 (1971) and the Supreme Court's decision in Weinberger v. Hynson, Westcott and Dunning, 412 U.S. 609 (1973). Both those cases place the burden of proffering substantial evidence of effectiveness on the NDA holder whose drug's efficacy has been called into question pursuant to the provisions of 21 U.S.C. 355(e).

In fact the notice of opportunity for hearing which initiated the proceedings in Weinberger v. Hynson, Westcott and Dunning, 412 U.S. 609 (1973), is indistinguishable from the notice of opportunity for hearing which initiated the proceedings in the instant case. Compare 34 Fed.Reg. 5556 (March 22, 1969) with 34 Fed.Reg. 19389 (December 6, 1969). It presented no more information with respect to the drug involved in that case (Lutrexin) than was presented for the drug involved in this case (Alevaire).

In its decision in Hynson, all but one member of the Supreme Court directly affirmed the validity of the notice of opportunity for hearing which initiated the proceedings involved in the case and the procedure used by FDA. (Mr. Justice Powell concurred in the result but did not concur with the other six Justices that the notice and the procedure followed by FDA were valid.)^{2/}

Of course, for reasons stated above, the government asserts that the Hess and Clark opinion was intended by Judge Levanthal to be limited to a safety withdrawal and is not in conflict with either the Supreme Court's opinion in Hynson or the opinion of this Court in Ciba-Geigy.

^{2/} There is no question that the issue of adequacy of notice and validity of the FDA's withdrawal procedure was before the Supreme Court; the issue was discussed at length in five of the briefs (including three amicus briefs which were largely devoted to only this issue) and orally argued before the Court.

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D.

Petitioners argue in paragraphs "3" and "5" of their letter that the Commissioner changed his rationale between issuing the March, 1973, withdrawal order and issuing the August, 1973, withdrawal order. On the contrary, the Commissioner has contended consistently since issuing his notice of intention to withdraw in July of 1968 that the ingredients of "Alevaire" have not been shown by petitioners to be effective and that the Miller-Paez and Cohen studies are not adequate to prove effectiveness. Indeed the Palmer study introduced into this proceeding by the HAS-NRC report issued in 1968, showed "Alevaire" to be no more effective than a combination of its ingredients less its alleged active ingredient, Tyloxapol. In the case at bar, the Commissioner has not relied on any information not available to the petitioners in excess of five years prior to the issuance of the August, 1973, order.

In paragraph "2" of petitioners' letter, they suggest that the Commissioner's August withdrawal order should be stricken because it was entered after the record in this case had been closed. In reply we can only say that the Court explicitly permitted the issuance of the August order and provided the government three weeks in which to issue it.

Respectfully submitted,

ROBERT V. ALLEN
Attorney for Respondents

cc: James Swire, Esquire

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 221

RECEIVED
FEBRUARY 20 1974

February 20, 1974

Honorable Daniel Fusaro
Clerk
United States Court of Appeals
United States Courthouse
Foley Square
New York, New York

Re: Sterling Drug Inc., et al. v.
Weinberger, et al., 73 -
1628, 2481

Dear Mr. Fusaro:

This is in reply to respondents' letter to the Court,
dated February 12, 1974.

Respondents attempt to distinguish Hess & Clark,
Division of Rhodia, Inc. v. Food & Drug Administration, 73-1589
(D.C. Cir. January 24, 1971) as a safety case, whereas the case
at bar involves effectiveness. Such a distinction could hardly
support respondents' position since, if anything, the Commissioner
would be expected to have more latitude in a case involving
safety. Indeed, Hess & Clark involved carcinogens. In any event,
the court there made clear that:

"[T]he ultimate principle is the same for both
issues [safety or efficacy] - that where the
case is governed by a statutory requirement for
hearing that hearing is not to be denied in
the absence of a fair opportunity to identify
material issues that require a hearing, an
opportunity that embraces a suitable notice of

PL. REPLY TO DEF. POST-TRIAL MEMO
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Honorable Daniel Fusaro
Clark
February 28, 1974
Page Two

the basis on which the agency proposes to
act summarily." (Slip op., 16).

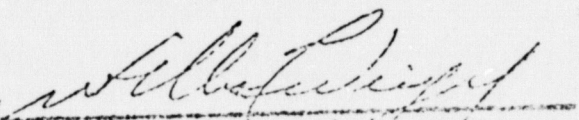
Respondents imply in Part "D" of their letter that, notwithstanding the lack of specific notice, the Palmer study constituted some sort of constructive notice which would support the August order at issue in Docket 73-2431. This is not true. Palmer studied Alevaire minus its active ingredient tyloxapol. He did not study tyloxapol versus sodium bicarbonate versus glycerin as the August order would require. Accordingly, his study is relevant only to the March order (A462) which has been fully rebutted by petitioners (see, for example, A436-437) and abandoned by FDA.

There is no "new information" upon which the Commissioner could or did rely to warrant applying the "fixed-combination" policy to Alevaire. FDA's proposed policy concerning fixed-combinations was based on the principle that "it is generally advisable to administer therapeutic agents separately ..." FDA's Proposed Statement Amplifying Policy on Drugs in Fixed Combinations, (February 13, 1971) (copy attached). In light of the concessions on oral argument by respondents' counsel as to the nature of the contributions of sodium bicarbonate and glycerin to Alevaire, it is clear that these ingredients are not in themselves mucco-evacuant agents. Hence, they are not pharmaceutically active in Alevaire. Accordingly, the fixed-combination policy is inapplicable to this drug.

Since respondents, through counsel, have also conceded that petitioners' studies are adequate and well-controlled, Alevaire's effectiveness is established and unrebutted. It is thus appropriate that the Commissioner's orders be set aside on the merits or, in the alternative, that an evidentiary hearing be convened.

Respectfully submitted,

ROGERS HOGE & HILLS

By 
Attorneys for Petitioners

attachment

By Hand

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 223

PROPOSED RULE MAKING

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

COMBINATION DRUGS FOR HUMAN
USE

Proposed Statement Amplifying Policy
on Drugs in Fixed Combinations

The Commissioner of Food and Drugs after considering a number of reports from panels of the NAS-NRC Drug Efficacy Study, the large numbers of combination drugs available, and those proposed for marketing, is of the opinion that criteria for rational combination drugs should be published for the guidance of the regulated industry. This statement is intended as amplification of the requirement that a new drug or antibiotic drug application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect which the drug combination is represented to have and purports to possess.

The problem of fixed combinations has been discussed with a number of experts; it is the subject of extensive discussion by experts in the medical literature. It is the consensus of these informed experts that a fixed dose combination drug must have an advantage to the patient over and above that obtained when one of the individual ingredients is used in the usual safe and effective dose. No drug should be present in a fixed combination unless its inclusion clearly enhances safety or efficacy and the fixed ratio of doses is safe and effective for all indications and for patients requiring such concurrent therapy. There are marketed combination drugs which meet these criteria. Many do not. Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended, 507, 59 Stat. 403, as amended, sec. 701 (a), 52 Stat. 1055; 21 U.S.C. 352, 355, 357, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that Part 3 be amended by adding thereto the following new section:

§ 3. --- Drugs for human use in fixed combinations.

(a) In implementing the provision of the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug, and

Cosmetic Act, which requires that a new drug and an antibiotic drug be shown effective for its labeled indications through adequate and well controlled clinical investigations by qualified experts, the Food and Drug Administration has found the unique problems presented by fixed combinations to require a more clearly defined position on such drugs.

(b) Fixed combinations represent a significant proportion of all marketed drugs. A 1969 survey indicated that of the 200 most widely used prescription drugs, approximately 40 percent were fixed combination dosage forms. Over-the-counter drugs are for the most part combination drugs.

(c) The Council on Drugs of the American Medical Association has consistently expressed the need for a sound medical rationale for using drugs in fixed combinations and has recently reaffirmed its longstanding position that the use of fixed-ratio combination drugs, antibiotics included, is with few exceptions neither a sound nor judicious practice. The United States Pharmacopeia has long had a policy against inclusion of combination drugs.

(d) The National Academy of Sciences-National Research Council in its reevaluation of all drugs marketed through the new-drug procedures between 1938 and 1962 to determine if the products were effective for all their labeled indications has clearly indicated the limitations in medical practice of fixed combination drugs. As a result of their recommendations, a number of widely used fixed antibiotic combinations have been removed from the market.

(e) The complexities of the problems were apparent to the Food and Drug Administration in evaluating several hundred fixed combination drugs in the Drug Efficacy Study; through the review of pending new drug applications and Notices of Claimed Exemption for Investigational Drugs, and in reviewing the labeling of other marketed drugs. Policies resulting from consideration of these problems would have significant impact on the pattern of medical practice. As a result, an Ad Hoc Committee was convened, consisting of outstanding experts representative of a cross section of medical disciplines, to assist in formulating the most scientifically sound guidelines for general application to determine when a fixed combination drug is rational. In addition, an Ad Hoc Committee consisting of members of the American Society of Pharmacology and Experimental Therapeutics prepared

recommendations on this problem at the request of the Food and Drug Administration.

(i) It is recognized that fixed combination drugs have or may have certain advantages, in addition to enhanced safety or efficacy, over use of the individual ingredients. These include:

(1) Better adherence to a therapeutic regimen, greater patient convenience, and greater economy than if each of the ingredients were given separately but concurrently.

(2) Availability of information on biopharmaceutical compatibility or unanticipated drug interactions.

(g) However, fixed combination drugs also present disadvantages to their use. The most common objections to these products are:

(1) Lack of flexibility to adjust the dosage of each component to the individual patient's needs.

(2) Exposure of patients to unnecessary drugs when one drug component alone would be effective.

(3) Increased possibility of adverse reactions without increased efficacy.

(h) Based on the above considerations, and in line with the recommendations of expert advisors and sound principles of medical practice, the Food and Drug Administration concludes:

(1) The concomitant administration of two or more medicinal agents may be indicated in the treatment of a patient. However, the effects of drugs are intrinsically so complex that it is generally advisable to administer therapeutic agents separately in order that the dosage and frequency of administration of the individual drugs may be varied in accordance with the patient's requirements.

(2) A combination of drugs in one product suggests and implies an added usefulness over one component alone. The implied or suggested usefulness, as well as the claims in the labeling of a drug, must be considered by the Food and Drug Administration in its evaluation of the validity of labeling claims.

(3) Fixed combinations of drugs may be approved where there is evidence of safety and substantial evidence of effectiveness showing that each active component contributes to the effect claimed for the product in the following circumstances:

(i) Where components are combined to:

(a) Enhance efficacy (increase potency, prolong duration of effect, etc.), or
(b) Enhance safety (decrease the incidence or severity of adverse reactions), or

(c) Prevent abuse or misuse.

(ii) Or where components would be given concurrently and the dosage (amount and interval of administration) of each component is such that the fixed combination is safe and effective for patients requiring such concurrent therapy. The advantage of the combination must obtain for all conditions for which it is labeled, for the various dose schedules recommended, for the duration of dosage suggested, and for most patients for which the product is recommended.

(iii) And studies demonstrate that the pharmaceutical compounding of the fixed combination does not interfere with the bioavailability of each of the ingredients as compared with administration of the individual ingredients separately but concurrently.

(iv) In the event that a combination, presently the subject of an approved NDA or antibiotic monograph, has not been recognized as effective by the Commissioner based on his evaluation of the appropriate NAS/NRC panel report, or for which substantial evidence of effectiveness has not otherwise been presented, formulation, labeling or dosage changes may be proposed and any resulting combination may meet the appropriate criteria listed above.

Interested persons may, within 30 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-02, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: February 16, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 71-2283 Filed 2-17-71; 8:52 am]

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 225

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GDH:HSE
21-51-580

APR 24 1974

A. Daniel Fusaro, Clerk
United States Court of Appeals
for the Second Circuit
United States Courthouse
Foley Square
New York, New York 10007

Re: Sterling Drug, Inc., et al v. Weinberger,
et al., Nos. 73-1628 and 73-2481

Dear Mr. Fusaro:

On April 19, 1974, the Court of Appeals for the District of Columbia Circuit issued its opinion in Cooper Laboratories, Inc. v. Commissioner (No. 72-1866). We believe this decision is relevant to issues raised by petitioners in the captioned case, especially the issue of adequate notice provided to an NDA holder (Sterling's "Alevaire" in this case) upon Food and Drug Administration notice of intended withdrawal for lack of substantial evidence of effectiveness.

Sterling has twice (see pet. br. and letter dated January 21, 1974) argued that this Court should follow the suggestion in USV Pharmaceutical Corp. v. Secretary, 466 F.2d 455 (D.C. Cir. 1972) that "it is FDA's burden in the first instance to make a prima facie case in detail that would warrant withdrawal" (letter of January 29, 1974, p. 2).

In Cooper, the District of Columbia Circuit has expressly repudiated its earlier position in light of the Supreme Court's decision in Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973). Slip op., n. 22 at pp. 15-16, and accompanying text.

PL. REPLY TO DEF. POST-TRIAL MEMO
A. 226

We have enclosed four copies of the Cooper slip opinion and respectfully request that these copies and this letter be forwarded to the panel which has this case sub judice.

Very truly yours,

HE

HOWARD S. EPSTEIN
Attorney for Respondents

cc: James Swire, Esq.

ORDER
A. 227

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----- X

SEBASTIAN BROS., INC., VENDOR
FARMERS, INC., and
MILWAUKEE, INC.,

Plaintiffs,

- v -

CASPAR W. WINTERKUN, Secretary
of Health, Education and Welfare,
and ALEXANDER H. SCHMIDT,
Commissioner of Food and Drugs,

Defendants.

----- X

CIVIL

74 Civ. 4282 (LMP)

The Court having denied plaintiffs' motion for a preliminary injunction and dismissed the complaint in a Memorandum Opinion dated and filed October 31, 1974, it is hereby

ORDERED that the complaint and action shall be and hereby is dismissed with costs to be taxed to plaintiffs.

Dated: New York, New York

Nov. 5, 1974

signed Lee P. Gallardi

~~LEONARD H. FARMER~~
United States District Judge

LEE P. GALLARDI

NOTICE OF APPEAL

A. 228

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----X

STERLING DRUG INC., WINTHROP	:	
PRODUCTS, INC. and BREON	:	
LABORATORIES, INC.,	:	
Plaintiffs,	:	74 Civ. 4282 (LWP)
-against-	:	<u>NOTICE OF APPEAL</u>
CASPAR W. WEINBERGER, Secretary	:	
of Health, Education and Welfare,	:	
and ALEXANDER M. SCHMIDT,	:	
Commissioner of Food and Drugs,	:	
Defendants.	:	

-----X

NOTICE IS HEREBY GIVEN that Sterling Drug Inc.,
Winthrop Products, Inc. and Breon Laboratories, Inc.,
plaintiffs above named, hereby appeal to the United States
Court of Appeals for the Second Circuit from the final
judgment entered in this action on the 6th day of November,
1974.

Dated: New York, New York
November 6, 1974

ROGERS HOGE & HILLS

By

James B. Hill
A Member of the Firm
Attorneys for Plaintiffs
Office and P. O. Address
90 Park Avenue
New York, New York 10016
(212) 953-9200

TO: CASPAR W. WEINBERGER
DEPARTMENT OF HEALTH +
EDUCATION & WELFARE
WASHINGTON, D.C.

ALEXANDER M. SCHMIDT,
COMMISSIONER OF FOOD & DRUGS
5600 FISHERS LANE
ROCKVILLE, MARYLAND

PAUL CURRAN
U.S. ATTORNEY
U.S. COURTHOUSE
NEW YORK, N.Y.

Paul J. Curran (RL)

COPY RECEIVED

November 26, 1974

UNITED STATES ATTORNEY